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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Prostate Cancer**

Version 1.2018 — February 14, 2018

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

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**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/physician.html](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

Updates in Version 1.2018 of the NCCN Guidelines for Prostate Cancer from Version 2.2017 include:

### [PROS-1](#)

- This page has been reformatted.
- Initial prostate cancer diagnosis, added a footnote linking to the [NCCN Guidelines for Prostate Cancer Early Detection](#).
- Initial prostate cancer diagnosis, added "Life expectancy estimation."
- Life expectancy ≤5 y and asymptomatic, divided the pathway based on risk groups.
- High or very high risk groups, added "Observation or ADT or EBRT."
- Life expectancy >5 y or symptomatic, added a link to [Risk Stratification and Staging Workup \(See PROS-2\)](#).
- Footnote "c" changed "The following should be considered" to "A *strong family history consists of*: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age; *known* germline DNA repair gene abnormalities, especially *BRCA2* mutation or Lynch syndrome (germline mutations in *MLH1*, *MSH2*, *MSH6*, or *PMS2*); and/or more than one relative with ~~strong family history~~ for breast, ovarian, or pancreatic cancer (suggests possibility of *BRCA2* mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome).

### [PROS-2](#)

- This is a new page, Risk Stratification and Staging Workup with associated footnotes ([PROS-3](#)).

### [PROS-3](#)

- Modified existing footnotes and added new ones as needed to correspond with new Risk Stratification and Staging Workup on [PROS-2](#).

### [PROS-4](#)

- Expected patient survival ≥ 20 y, removed "The panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. [See NCCN Guidelines for Prostate Cancer Early Detection](#). Active surveillance is recommended for these subsets of patients."
- Modified the link to "See Monitoring for Initial Definitive Therapy ([PROS-10](#))."
- Estimated patient survival <10 y, observation added a link to [See Monitoring \(PROS-10\)](#).

### [PROS-5](#)

- Expected patient survival ≥ 10 y, removed "The panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. [See NCCN Guidelines for Prostate Cancer Early Detection](#). Active surveillance is recommended for these subsets of patients."
- Estimated patient survival <10 y, observation added: [See Monitoring \(PROS-10\)](#).

### [PROS-6](#)

- Divided intermediate-risk group into 2 pages, "Favorable intermediate risk group" and "Unfavorable intermediate risk group" ([PROS-7](#)).
- Changed PSA failure to "PSA persistence/recurrence" throughout the guidelines.
- Favorable intermediate, expected patient survival ≥ 10 y, initial therapy:
  - ▶ Added "Active surveillance:
    - ♦ PSA no more often than every 6 mo unless clinically indicated
    - ♦ DRE no more often than every 12 mo unless clinically indicated
    - ♦ Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
    - ♦ Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative."
  - ▶ Removed options for EBRT + ADT, EBRT + brachytherapy, and EBRT + ADT + brachytherapy.
- Favorable intermediate: expected patient survival < 10 y, initial therapy:
  - ▶ Removed options for EBRT + ADT, EBRT + brachytherapy, and EBRT + ADT + brachytherapy.
- New footnote (applies to several pages): "PSA nadir is the lowest value reached."
- New footnote (applies to several pages): "PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence)."

### [PROS-7](#)

- Unfavorable intermediate risk group, expected patient survival ≥ 10 y and <10 y: removed options for EBRT alone and brachytherapy alone.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

Updates in Version 1.2018 of the NCCN Guidelines for Prostate Cancer from Version 2.2017 include:

### [PROS-8](#)

- Combined high and very high risk groups.
- Added "Expected patient survival > 5 y."
- ADT and observation were removed as options for patients with very high risk disease.
- Changed "EBRT + brachytherapy ± ADT (2-3 y)" to "EBRT + brachytherapy + ADT (1-3 y; category 1)."

### [PROS-9](#)

- Added "Expected patient survival > 5 y."
- Initial therapy, added "± abiraterone and prednisone" to EBRT and ADT recommendations.
- Options for metastatic disease were removed from this page.

### [PROS-10](#)

- Changed "bone scan" to "bone imaging" throughout the guidelines.
- Removed "or pathology" from heading.
- N1 or M1 on ADT, removed "or M1" and added "or localized on observation."
- New footnote "Treatment for patients who progressed on observation of localized disease is ADT."
- Modified footnote to progression (applies to several pages): "*Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation.*

[See Principles of Imaging \(PROS-B\)](#) and [Discussion](#).

- New footnote defining CRPC (also applies to [PROS-15](#)): "Castration resistant prostate cancer (CRPC) is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 008;26:1148-1159."

### [PROS-11](#)

- Changed page title from "Radical Prostatectomy Biochemical Failure" to "Radical Prostatectomy PSA Persistence/Recurrence."
- Consider chest x-ray, added "or chest CT."
- Changed "Consider bone scan" to "Consider bone imaging."
- Changed "Consider C-11 choline PET/CT" to "Consider C-11 choline or F-18

fluciclovine PET/CT or PET/MRI."

- New footnote (also applies to [PROS-12](#)): "F-18 sodium fluoride PET/CT can be considered after bone scan for further evaluation when clinical suspicion of bone metastases is high."
- New footnote (also applies to [PROS-12](#)): "Histologic confirmation is recommended whenever feasible due to significant rates of false positivity."
- Added: "Consider Decipher molecular assay (category 2B)".

### [PROS-12](#)

- Chest x-ray, added "or chest CT."
- Removed "consider" from "TRUS biopsy."
- Changed "Consider C-11 choline PET/CT" to "Consider C-11 choline or F-18 fluciclovine PET/CT or PET/MRI."

### [PROS-13](#)

- Changed page heading to "Systemic therapy for castration-naive disease."
- M1, ADT and docetaxel, removed "with or without prednisone" and added "(category 1)."
- M1, added "ADT and abiraterone with prednisone (category 1)."
- Added "Physical exam + PSA every 3-6 mo."
- Added "Bone imaging for symptoms and as often as every 6-12 mo."
- Moved branch for "Small cell" to page [PROS-17](#).

### [PROS-14](#)

- Changed "PSA rising" to "PSA increasing."
- Removed the following from the page: (included on [PROS-F](#))
  - ▶ Antiandrogen
  - ▶ Antiandrogen withdrawal
  - ▶ Ketoconazole ± hydrocortisone
  - ▶ Corticosteroid
  - ▶ DES or other estrogen

### [PROS-15](#)

- Added "Consider tumor testing for MSI-high (MSI-H) or dMMR."
- Added "Consider genetic counseling and germline testing for homologous recombination gene mutations."
- Added footnote "DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch





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## Prostate Cancer

### Updates in Version 1.2018 of the NCCN Guidelines for Prostate Cancer from Version 2.2017 include:

- syndrome. MSI-H or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC ([see PROS-16](#) and [PROS-17](#))."
  - Added footnote "Consider testing for mutation in these genes (germline and somatic): *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*; refer to genetic counseling if mutation is found. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors)."
  - Changed "Maintain castrate levels..." to "Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)."
  - Added a new bullet "Consider additional treatment options:"
    - ▶ Bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present.
    - ▶ Immunotherapy with sipuleucel-T (category 1), removed the following from the page (included on [See PROS-G](#)) "if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1."
  - Added a new footnote defining visceral metastases. "Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/ lymph node sites are not considered visceral."
  - No visceral metastases, removed "with prednisone" from docetaxel.
  - Added "other" to secondary hormone therapy.
- PROS-16**
- Prior therapy abiraterone/enzalutamide:
    - ▶ Removed "with prednisone" from docetaxel.
    - ▶ Added "Pembrolizumab for MSI-H or dMMR (category 2B)" (also applies to [PROS-17](#))
    - ▶ Added a bullet "If not previously received" before sipuleucel-T.
  - Prior therapy docetaxel:
    - ▶ Removed "with prednisone" from cabazitaxel.
    - ▶ Added "Pembrolizumab for MSI-H or dMMR (category 2B)."
    - ▶ Added a bullet "If not previously received" before abiraterone with prednisone, enzalutamide, or sipuleucel-T.
    - ▶ Added "consider" to docetaxel rechallenge.
    - ▶ Removed "alternative chemotherapy" before mitoxantrone with prednisone.
  - Added a new column "at progression" listing options "If not previously received."
  - New footnote: "Patients who received docetaxel with ADT in the metastatic castration-naïve setting can be considered for docetaxel rechallenge in the CRPC setting."
  - New footnote: "Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies."
- PROS-17**
- Removed "subsequent" from the title, "Systemic therapy for M1 CRPC."
  - Added a new heading "Subsequent therapy."
  - Added branch for "Small cell" previously on ([PROS-15](#))
  - Added "consider brain MRI with and without contrast" for small cell
  - Added "Consider biopsy."
  - New footnote: "Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed."
  - Added a branch for "adenocarcinoma."
  - New footnote: "Patients treated with first-line systemic therapy for non-visceral metastases ([see PROS-15](#)) should proceed to a different systemic therapy."
- PROS-B (1 of 3)**
- Bone imaging, removed "Newer technology using F-18 as the tracer for a PET/CT scan or hybrid imaging bone scan can be used as a diagnostic staging study. These tests appear to have greater sensitivity than bone scan. However, there is controversy about how the results of F-18 NaF PET/CT bone scan should be acted upon since all phase 3 clinical trials to date have used progression criteria on bone scans."
  - Removed "T1 disease and PSA ≥20, T2 disease and PSA ≥10, Gleason score ≥8, or T3/T4 disease" and "Any stage disease with symptoms suggestive of osseous metastatic disease."
  - Replaced with "Bone scan is indicated in the initial evaluation of patients at high risk for skeletal metastases. ([PROS-2](#))."
- PROS-B (2 of 3)**
- Added the following bullets:
    - ▶ PET/CT for detection of bone metastatic disease M0 CRPC
      - ◊ F-18 sodium fluoride PET/CT may be used to detect bone metastatic disease with greater sensitivity but less specificity than standard bone scan imaging.
      - ◊ Plain films, CT, MRI, or F-18 sodium fluoride PET/CT may be used after bone scan for further evaluation of equivocal findings.
      - ◊ Early detection of bone metastatic disease may result in earlier use of newer and more expensive therapies, which may not improve oncologic outcome or overall survival.



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## Prostate Cancer

### Updates in Version 1.2018 of the NCCN Guidelines for Prostate Cancer from Version 2.2017 include:

- Computed tomography, replaced the following bullets with a new bullet:
  - ▶ ~~CT is used for initial staging in select patients (PROS-2)~~
    - ◊ ~~T3 or T4 disease~~
    - ◊ ~~Patients with T1 or T2 disease and nomogram-indicated probability of lymph node involvement >10% may be candidates for pelvic imaging, but the level of evidence is low.~~
  - ▶ ~~CT may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy or systemic therapy.~~
  - ▶ Added "CT can be used for examination of the pelvis and/or abdomen for initial evaluation ([see PROS-2](#)) and as part of workup for recurrence or progression ([see PROS-11](#) through [PROS-17](#))."
- Magnetic resonance imaging, replaced the following bullets with a new bullet:
  - ▶ ~~Standard MRI techniques can be considered for initial evaluation of high-risk patients:~~
    - ◊ ~~T3 or T4 disease~~
    - ◊ ~~Patients with T1 or T2 disease and nomogram-indicated probability of lymph node involvement >10% may be candidates for pelvic imaging, but the level of evidence is low.~~
- Added "Standard MRI techniques can be used for examination of the pelvis and/or abdomen for initial evaluation ([see PROS-2](#)) and as part of workup for recurrence or progression ([see PROS-11](#) through [PROS-17](#))."

#### [PROS-B \(3 of 3\)](#)

- Updated previous section for positron emission tomography/computed tomography (PET/CT).
- Added a bullet defining Will Rogers effect.

#### [PROS-C \(2 of 2\)](#)

- Added mpMRI to "Period follow-up *mpMRI* and prostate biopsies may be necessary."

#### [PROS-D \(1 of 3\)](#)

- The Principles of Radiation Therapy was extensively revised. A new table of regimens was added.

#### [PROS-F \(1 of 4\)](#)

- Hormonal therapy options were revised for the following settings:
  - ▶ ADT for regional disease, adjuvant treatment of lymph node metastases, or patients on observation who require treatment.
  - ▶ Neoadjuvant, concurrent, and/or adjuvant ADT as part of radiation therapy for clinically localized disease.
  - ▶ ADT for M0 or M1 castration-naïve disease.
  - ▶ Secondary hormone therapy for M0 or M1 CRPC.
- Added a new footnote: "Ketoconazole ± hydrocortisone should not be used if disease progressed on abiraterone with prednisone."
- Secondary Hormone Therapy for M0 or M1 CRPC, added "abiraterone + prednisone" to the list of options. (was previously on PROS-F, 3 of 4)

#### [PROS-F \(4 of 4\)](#)

- Updated screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.

#### [PROS-G \(1 of 3\)](#)

- Systemic therapy for M1 CRPC:
  - ▶ Chemotherapy
    - ◊ ~~Docetaxel with concurrent steroid, + prednisone (category 1; category 2A for rechallenge)~~
      - Added, "Concurrent steroids may include: daily prednisone or dexamethasone on the day of chemotherapy."
    - ▶ Cabazitaxel with concurrent steroid, + prednisone (category 1; category 2A for rechallenge)
      - Added, "Concurrent steroids may include: daily prednisone or dexamethasone on the day of chemotherapy."
    - ▶ Sipuleucel-T (category 1)
    - ▶ Pembrolizumab (for MSI-H or dMMR)
      - ◊ *Only as subsequent systemic therapy for patients who have progressed through at least one line of systemic therapy for M1 CRPC.*

#### [STAGING](#)

- The staging tables were updated based on the AJCC Eighth Edition.

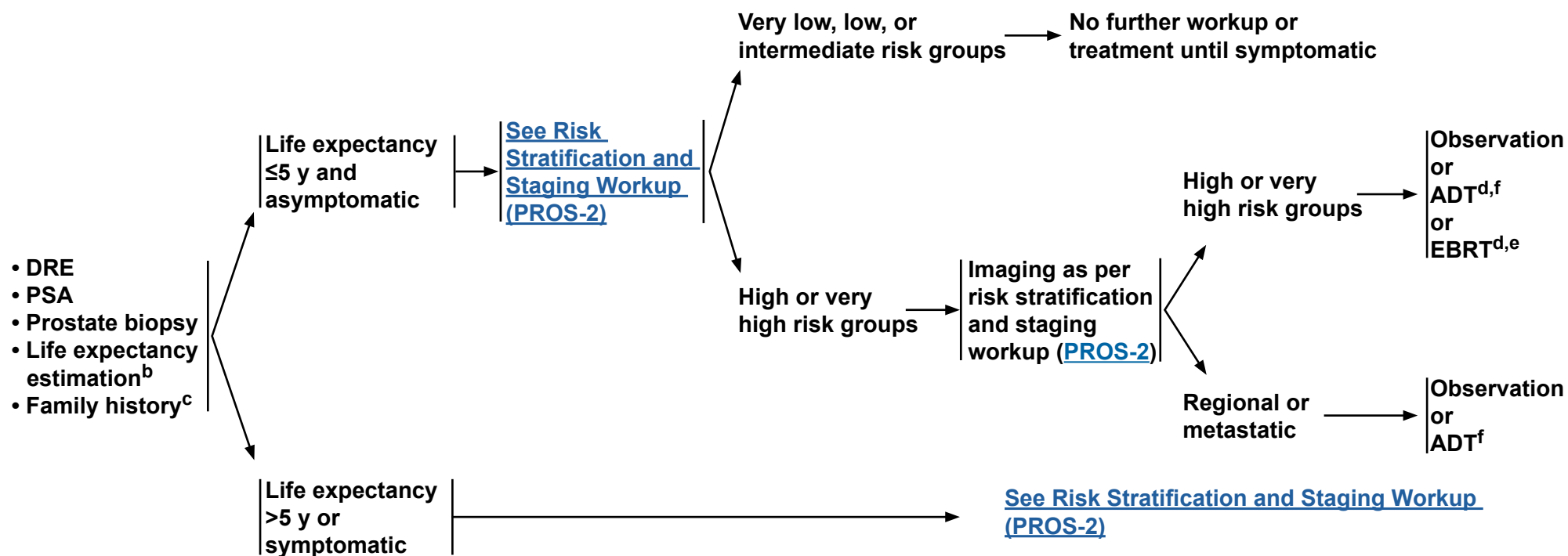


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## Prostate Cancer

### INITIAL PROSTATE CANCER DIAGNOSIS<sup>a</sup>

### INITIAL CLINICAL ASSESSMENT



<sup>a</sup>See NCCN Guidelines for Prostate Cancer Early Detection.

<sup>b</sup>See Principles of Life Expectancy Estimation (PROS-A).

<sup>c</sup>A strong family history consists of: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age; known germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2); and/or more than one relative with breast, ovarian, or pancreatic cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome).

<sup>d</sup>Androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered in selected patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastasis, can be expected within 5 y.

<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

**Note:** All recommendations are category 2A unless otherwise indicated.

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## Prostate Cancer

### RISK STRATIFICATION AND STAGING WORKUP

Risk group	Clinical/pathologic features	Imaging <sup>i,j</sup>	Molecular testing of tumor	Germline testing	Initial therapy <sup>p</sup>
Very low <sup>g</sup>	<ul style="list-style-type: none"> <li>• T1c AND</li> <li>• Gleason score ≤6/grade group 1 AND</li> <li>• PSA &lt;10 ng/mL AND</li> <li>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core<sup>h</sup> AND</li> <li>• PSA density &lt;0.15 ng/mL/g</li> </ul>	Not indicated	Not indicated	Consider if strong family history <sup>c</sup>	<a href="#">See PROS-4</a>
Low <sup>g</sup>	<ul style="list-style-type: none"> <li>• T1-T2a AND</li> <li>• Gleason score ≤6/grade group 1 AND</li> <li>• PSA &lt;10 ng/mL</li> </ul>	Not indicated	Consider if life expectancy ≥10y <sup>l</sup>	Consider if strong family history <sup>c</sup>	<a href="#">See PROS-5</a>
Favorable intermediate <sup>g</sup>	<ul style="list-style-type: none"> <li>• T2b-T2c OR</li> <li>• Gleason score 3+4=7/grade group 2 OR</li> <li>• PSA 10–20 ng/mL AND</li> <li>• Percentage of positive biopsy cores &lt;50%</li> </ul>	<ul style="list-style-type: none"> <li>• Bone imaging<sup>k</sup>: not recommended for staging</li> <li>• Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</li> </ul>	Consider if life expectancy ≥10y <sup>l</sup>	Consider if strong family history <sup>c</sup>	<a href="#">See PROS-6</a>
Unfavorable intermediate <sup>g</sup>	<ul style="list-style-type: none"> <li>• T2b-T2c OR</li> <li>• Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR</li> <li>• PSA 10–20 ng/mL</li> </ul>	<ul style="list-style-type: none"> <li>• Bone imaging<sup>k</sup>: recommended if T2 and PSA &gt;10 ng/mL</li> <li>• Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</li> </ul>	Not routinely recommended	Consider if strong family history <sup>c</sup>	<a href="#">See PROS-7</a>
High	<ul style="list-style-type: none"> <li>• T3a OR</li> <li>• Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR</li> <li>• PSA &gt;20 ng/mL</li> </ul>	<ul style="list-style-type: none"> <li>• Bone imaging<sup>k</sup>: recommended</li> <li>• Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</li> </ul>	Not routinely recommended	Consider <sup>o</sup>	<a href="#">See PROS-8<sup>p</sup></a>
Very high	<ul style="list-style-type: none"> <li>• T3b-T4 OR</li> <li>• Primary Gleason pattern 5 OR</li> <li>• &gt;4 cores with Gleason score 8–10/ grade group 4 or 5</li> </ul>	<ul style="list-style-type: none"> <li>• Bone imaging<sup>k</sup>: recommended</li> <li>• Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</li> </ul>	Not routinely recommended	Consider <sup>o</sup>	<a href="#">See PROS-8<sup>p</sup></a>
Regional	Any T, N1, M0	Already performed	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR) <sup>m,n</sup>	Consider <sup>o</sup>	<a href="#">See PROS-9</a>
Metastatic	Any T, Any N, M1	Already performed	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR <sup>m,n</sup>	Consider <sup>o</sup>	<a href="#">See PROS-13</a>

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[See footnotes on next page](#)



### RISK STRATIFICATION AND STAGING WORKUP FOOTNOTES

<sup>c</sup>Strong family history consists of: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age; known germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2); and/or more than one relative with breast, ovarian, or pancreatic cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome).

<sup>g</sup>For asymptomatic patients with life expectancy  $\leq 5$  years, no further workup or treatment is indicated until the patient becomes symptomatic.

<sup>h</sup>Patients with a MRI lesion that is biopsied and demonstrates grade group 1 cancer (regardless of percentage core involvement or number of cores involved) who otherwise qualify for very low risk should be considered very low risk.

<sup>i</sup>[See Principles of Imaging \(PROS-B\).](#)

<sup>j</sup>Bone imaging should be performed for any patient with symptoms consistent with bone metastases.

<sup>k</sup>Plain films, CT, MRI, or F-18 NaF PET/CT can be considered for equivocal results on initial bone scan. [See PROS-B.](#)

<sup>l</sup>Men with low or favorable intermediate risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, Promark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. [See Discussion.](#)

<sup>m</sup>DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC ([see PROS-16](#) and [PROS-17](#)).

<sup>n</sup>Consider testing for mutation in these genes (germline and somatic): *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*; refer to genetic counseling if positive. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors)

<sup>o</sup>The prevalence of inherited homologous recombination gene mutations in men with metastatic or localized high risk was found to be 11.8% and 6.0%, respectively. Therefore, germline genetic testing and genetic counseling should be considered in all men with high risk, very high risk, regional, or metastatic prostate cancer. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375:443-453.

<sup>p</sup>For asymptomatic patients with life expectancy  $\leq 5$  years, [See PROS-1.](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

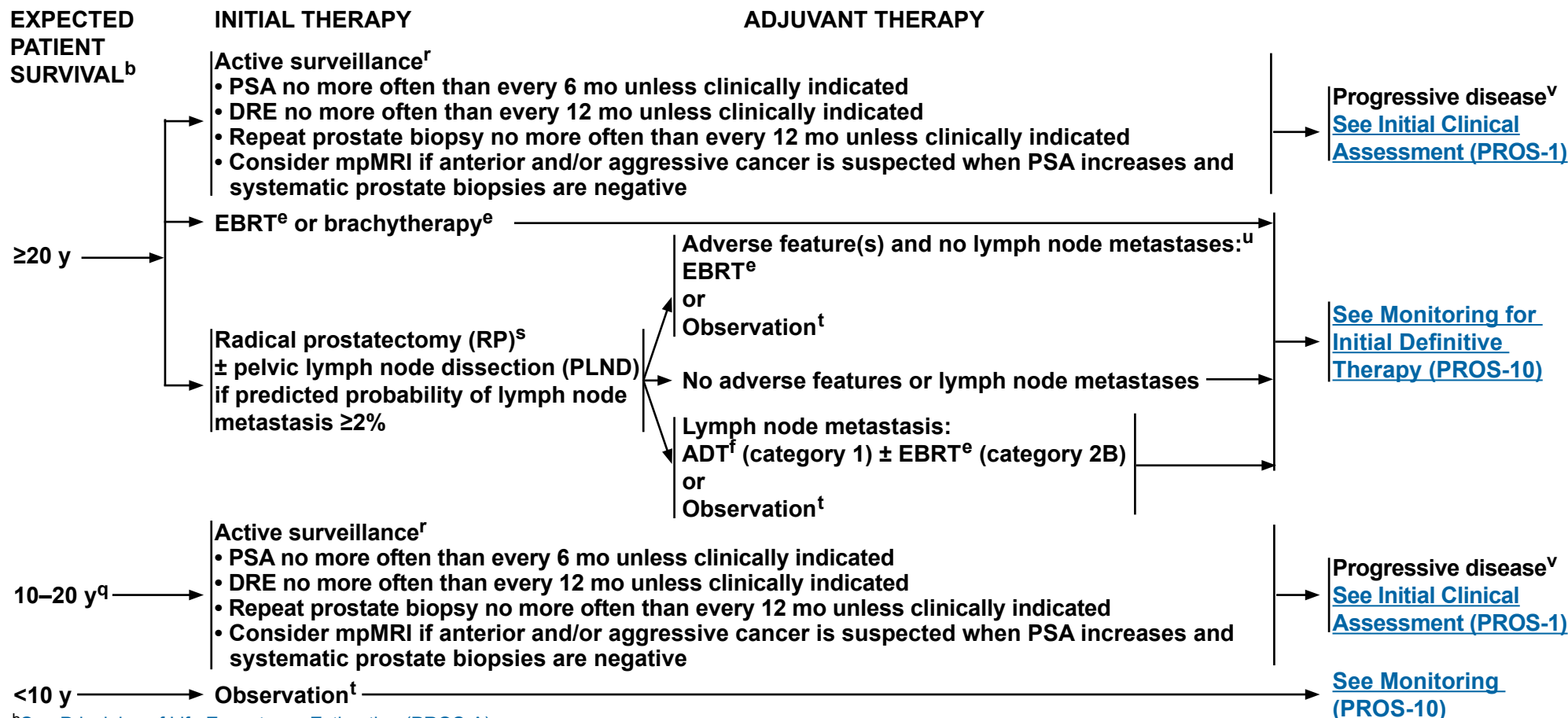
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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### VERY LOW RISK GROUP

<sup>b</sup>See Principles of Life Expectancy Estimation (PROS-A).<sup>e</sup>See Principles of Radiation Therapy (PROS-D).<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).<sup>q</sup>The panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. [See NCCN Guidelines for Prostate Cancer Early Detection](#). Active surveillance is recommended for these subsets of patients.<sup>r</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. [See Principles of Active Surveillance and Observation \(PROS-C\)](#).<sup>s</sup>See Principles of Surgery (PROS-E).<sup>t</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. [See Principles of Active Surveillance and Observation \(PROS-C\)](#).<sup>u</sup>Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.<sup>v</sup>Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. [See Discussion](#).**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



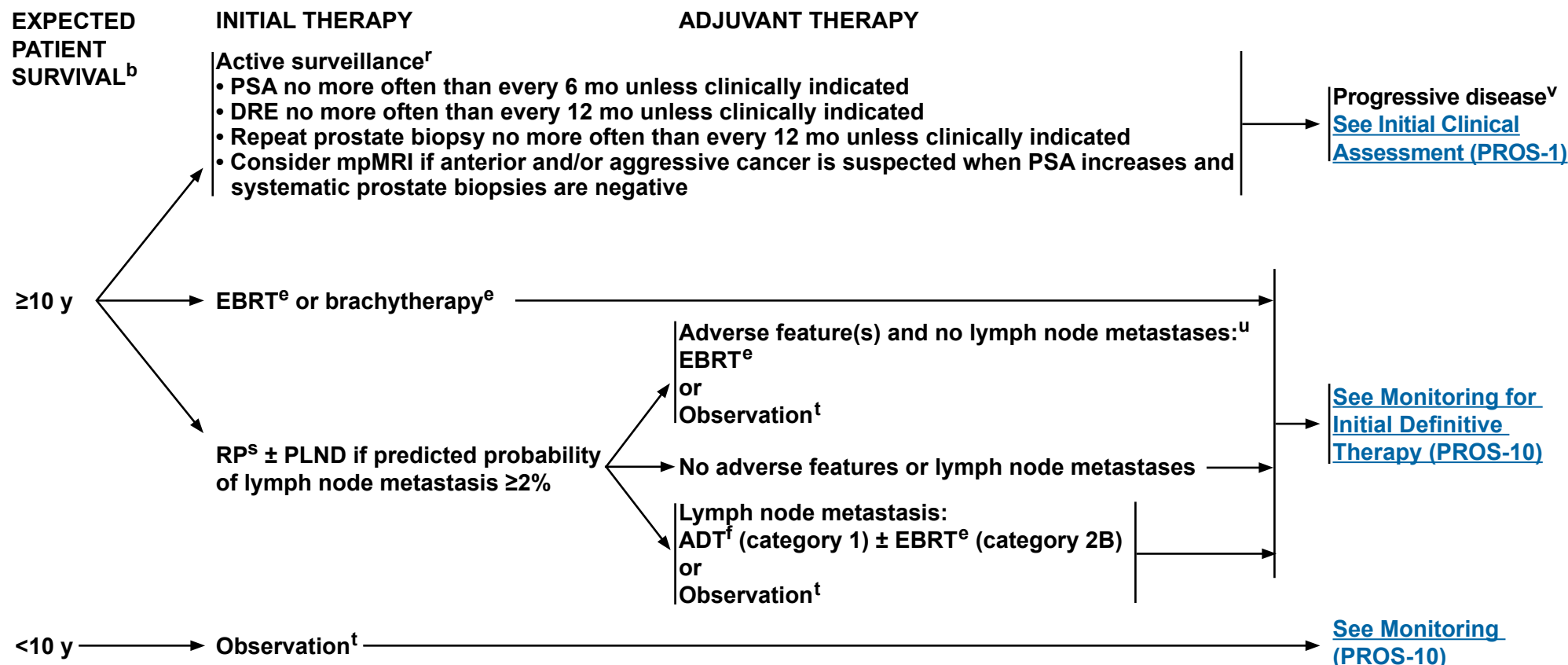
National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 1.2018

## Prostate Cancer

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[Discussion](#)

### LOW RISK GROUP



<sup>b</sup>[See Principles of Life Expectancy Estimation \(PROS-A\).](#)

<sup>e</sup>[See Principles of Radiation Therapy \(PROS-D\).](#)

<sup>f</sup>[See Principles of Androgen Deprivation Therapy \(PROS-F\).](#)

<sup>r</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. [See Principles of Active Surveillance and Observation \(PROS-C\).](#)

<sup>s</sup>[See Principles of Surgery \(PROS-E\).](#)

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. [See Principles of Active Surveillance and Observation \(PROS-C\).](#)

<sup>u</sup>Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.

<sup>v</sup>Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. [See Discussion.](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

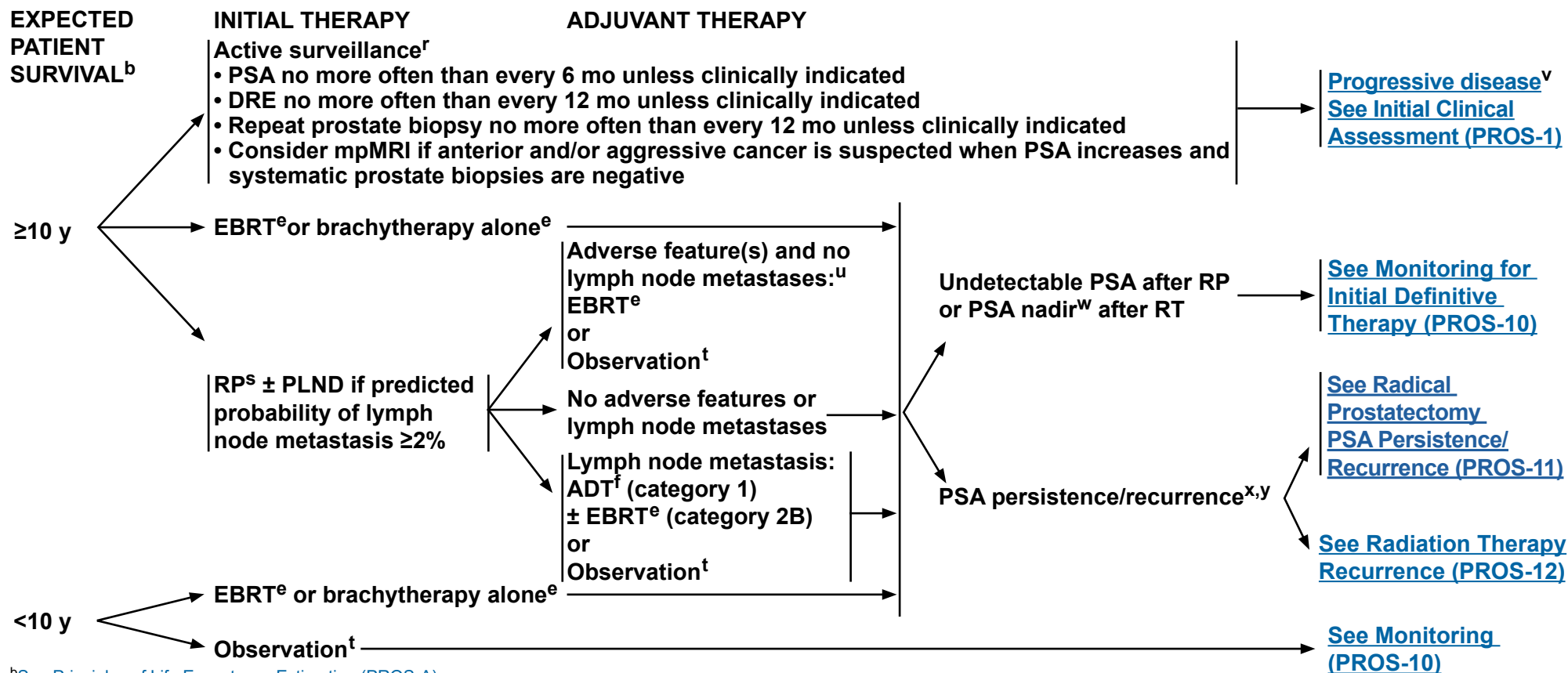
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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### FAVORABLE INTERMEDIATE RISK GROUP

<sup>b</sup>See [Principles of Life Expectancy Estimation \(PROS-A\)](#).<sup>e</sup>See [Principles of Radiation Therapy \(PROS-D\)](#).<sup>f</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).<sup>r</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).<sup>s</sup>See [Principles of Surgery \(PROS-E\)](#).<sup>t</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).<sup>u</sup>Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.<sup>v</sup>Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. See [Discussion](#).<sup>w</sup>PSA nadir is the lowest value reached.<sup>x</sup>PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).<sup>y</sup>RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA persistence/recurrence after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

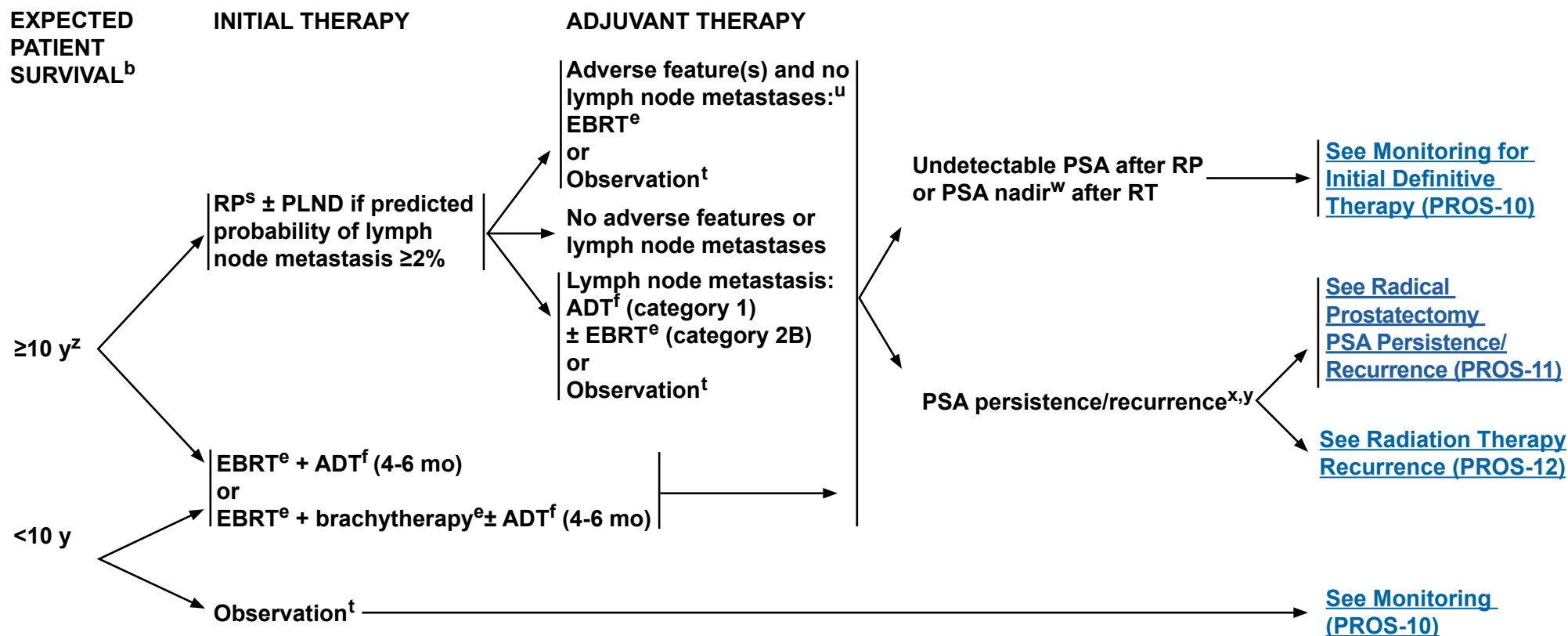




# NCCN Guidelines Version 1.2018

## Prostate Cancer

### UNFAVORABLE INTERMEDIATE RISK GROUP


<sup>b</sup>See Principles of Life Expectancy Estimation (PROS-A).

<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>s</sup>See Principles of Surgery (PROS-E).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).

<sup>u</sup>Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.

<sup>w</sup>PSA nadir is the lowest value reached.

<sup>x</sup>PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).

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<sup>z</sup>Active surveillance of unfavorable intermediate and high risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

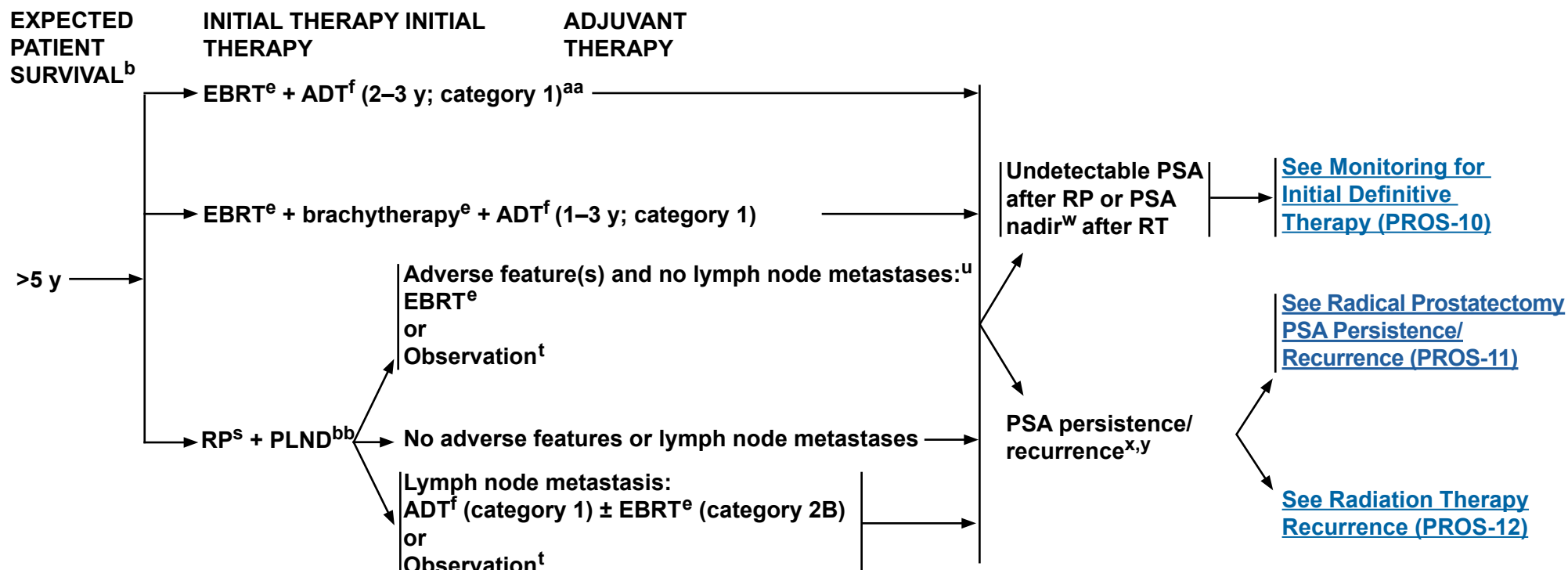
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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### HIGH or VERY HIGH RISK GROUP


<sup>b</sup>See Principles of Life Expectancy Estimation (PROS-A).

<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>s</sup>See Principles of Surgery (PROS-E).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. [See Principles of Active Surveillance and Observation \(PROS-C\)](#).

<sup>u</sup>Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.

<sup>w</sup>PSA nadir is the lowest value reached.

<sup>x</sup>PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).

YRTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA persistence/recurrence after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

<sup>aa</sup>Six cycles of docetaxel every 3 weeks with concurrent steroid may be administered after completion of radiation in selected patients who are fit for chemotherapy.

<sup>bb</sup>RP + PLND can be considered in younger, healthier patients without tumor fixation to the pelvic side-wall.

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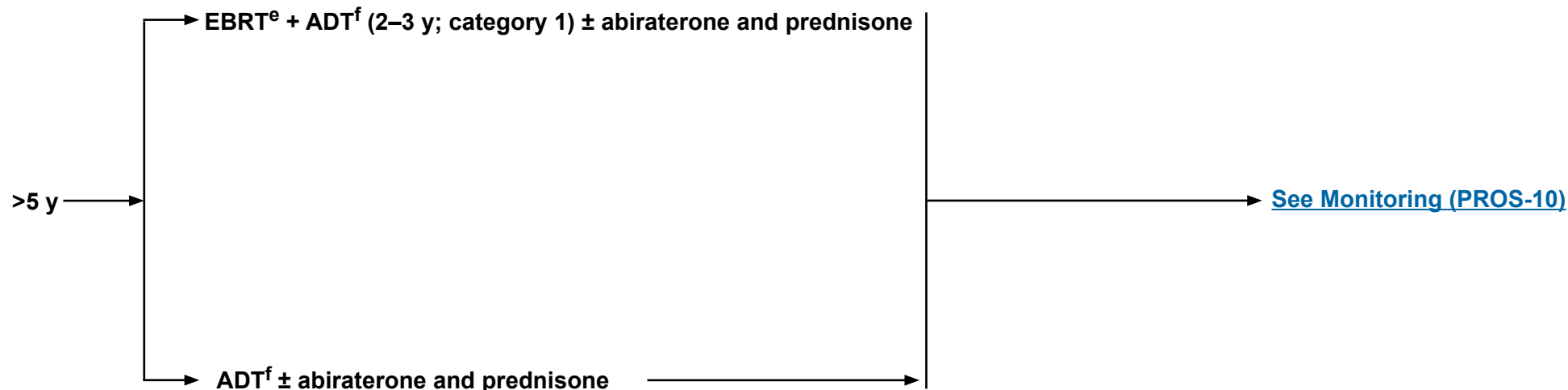
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### REGIONAL RISK GROUP

EXPECTED  
PATIENT  
SURVIVAL<sup>b</sup>

INITIAL THERAPY



<sup>b</sup>[See Principles of Life Expectancy Estimation \(PROS-A\).](#)

<sup>e</sup>[See Principles of Radiation Therapy \(PROS-D\).](#)

<sup>f</sup>[See Principles of Androgen Deprivation Therapy \(PROS-F\).](#)

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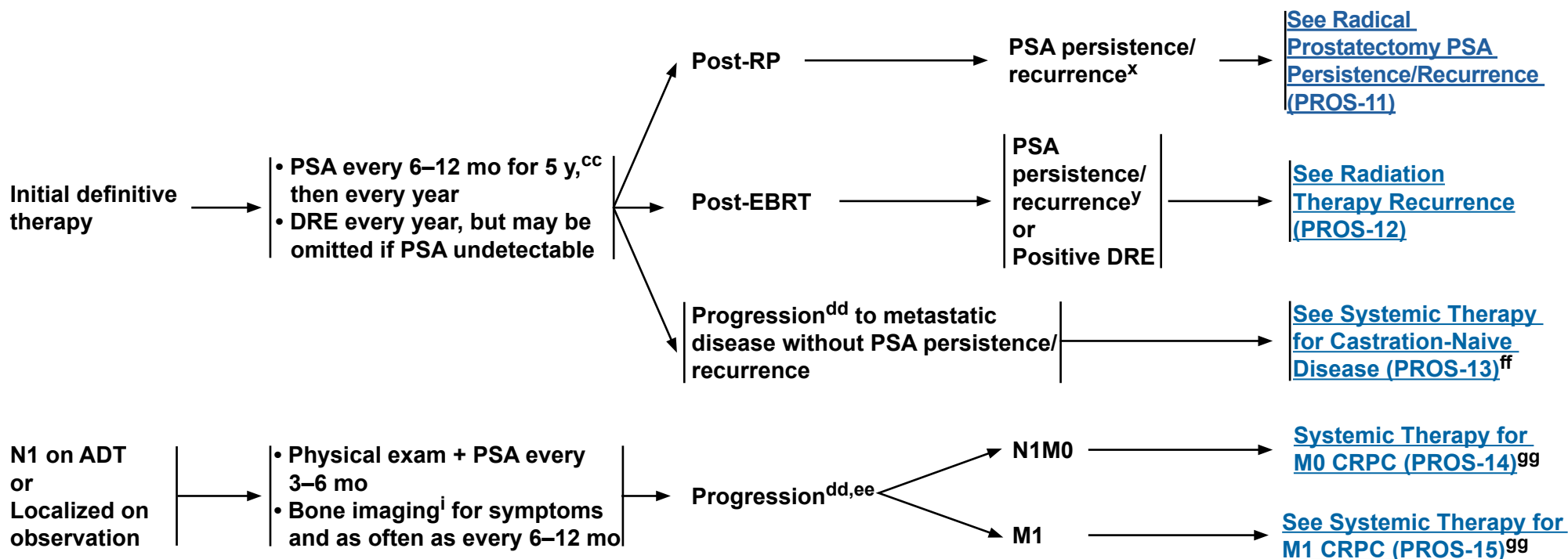
# NCCN Guidelines Version 1.2018

## Prostate Cancer

### INITIAL MANAGEMENT

### MONITORING

### RECURRENCE



<sup>i</sup>[See Principles of Imaging \(PROS-B\)](#).

<sup>x</sup>PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).

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<sup>cc</sup>PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.

<sup>dd</sup>Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. [See Principles of Imaging \(PROS-B\)](#) and [Discussion](#).

<sup>ee</sup>Treatment for patients who progressed on observation of localized disease is ADT.

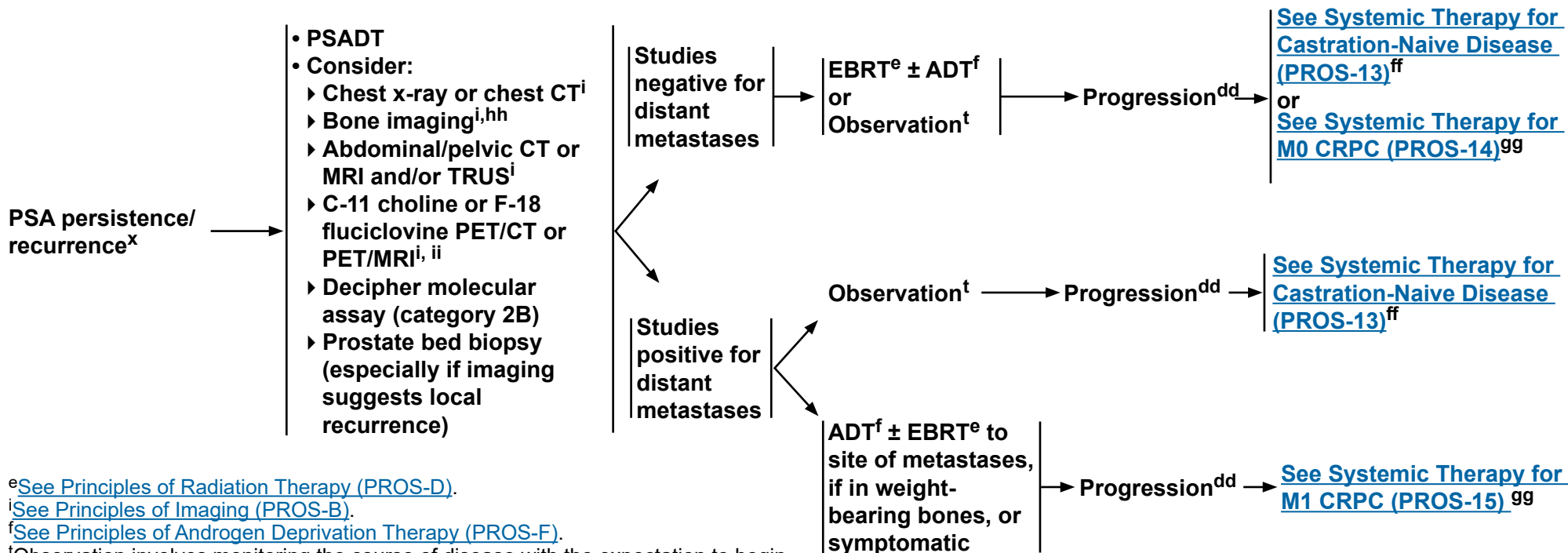
<sup>ff</sup>The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

<sup>99</sup>Castration-resistant prostate cancer (CRPC) is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-1159.

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**RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE**



<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>i</sup>See Principles of Imaging (PROS-B).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent.

See Principles of Active Surveillance and Observation (PROS-C).

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<sup>ff</sup>The term "castration-naïve" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naïve" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

<sup>gg</sup>Castration-resistant prostate cancer (CRPC) is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-1159.

<sup>hh</sup>F-18 sodium fluoride PET/CT can be considered after bone scan for further evaluation when clinical suspicion of bone metastases is high.

<sup>ii</sup>Histologic confirmation is recommended whenever feasible due to significant rates of false positivity.

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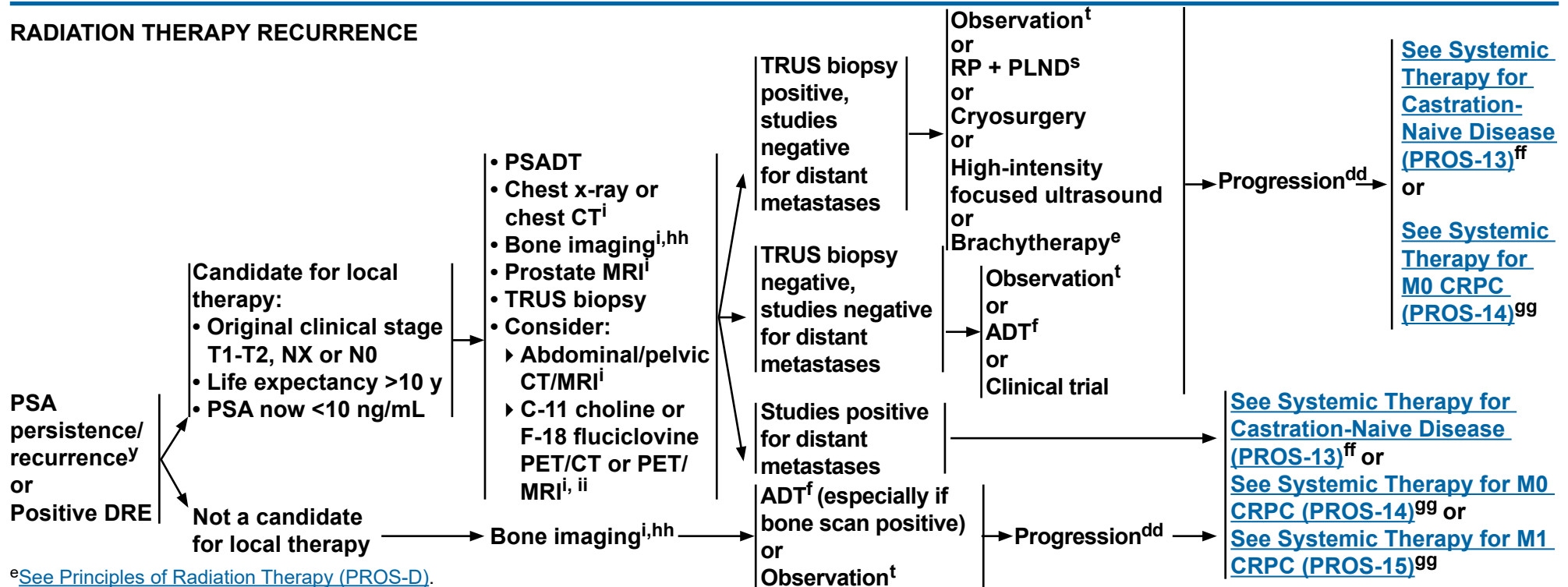




# NCCN Guidelines Version 1.2018

## Prostate Cancer

### RADIATION THERAPY RECURRENCE



<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>i</sup>See Principles of Imaging (PROS-B).

<sup>s</sup>See Principles of Surgery (PROS-E).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. [See Principles of Active Surveillance and Observation \(PROS-C\).](#)

<sup>v</sup>RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA persistence/recurrence after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

<sup>dd</sup>Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT

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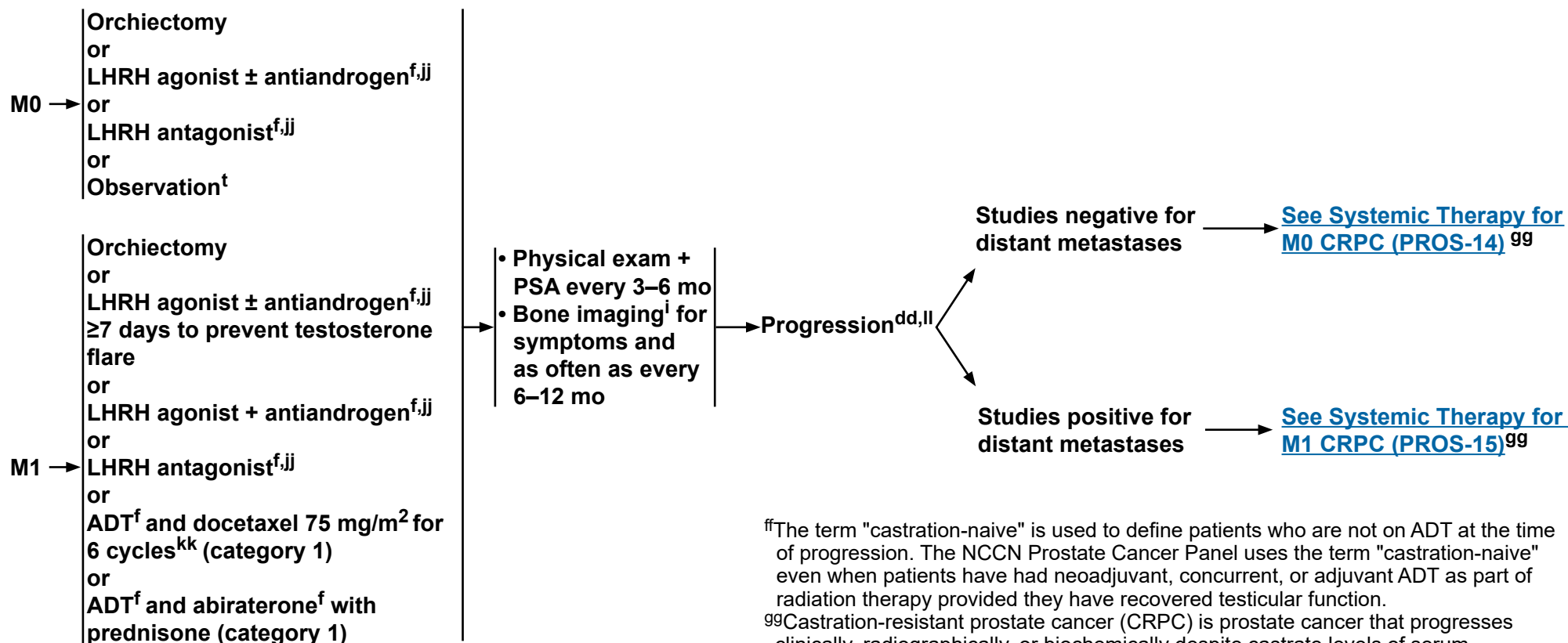
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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### SYSTEMIC THERAPY FOR CASTRATION-NAIVE DISEASE<sup>ff</sup>



<sup>f</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>i</sup>See [Principles of Imaging \(PROS-B\)](#).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).

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<sup>jj</sup>Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>kk</sup>High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

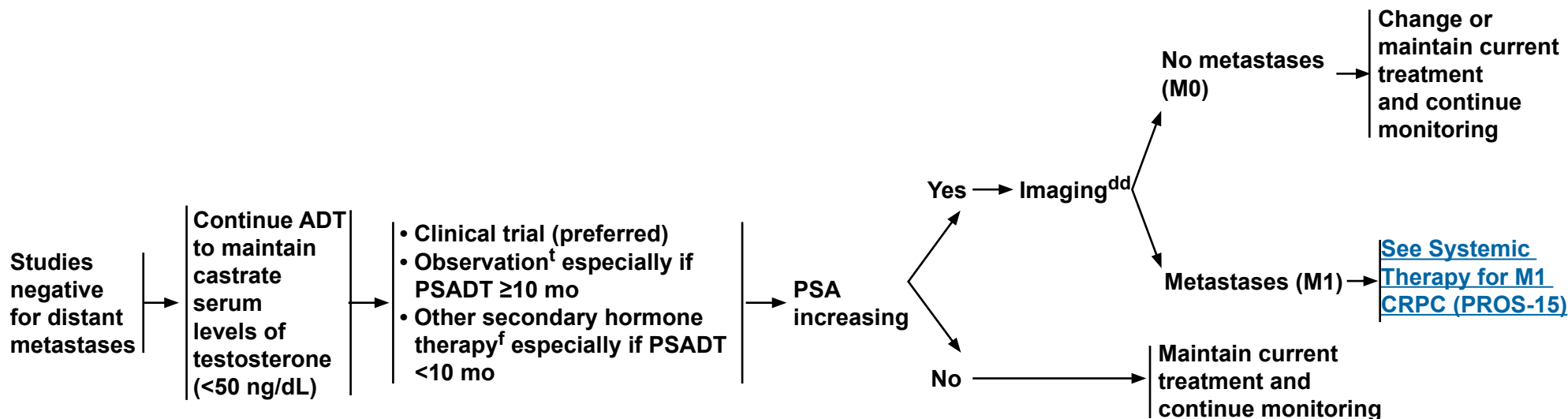
<sup>ll</sup>Assure castrate level of testosterone.

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### SYSTEMIC THERAPY FOR M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)<sup>99</sup>



<sup>f</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>t</sup>Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent.

See [Principles of Active Surveillance and Observation \(PROS-C\)](#).

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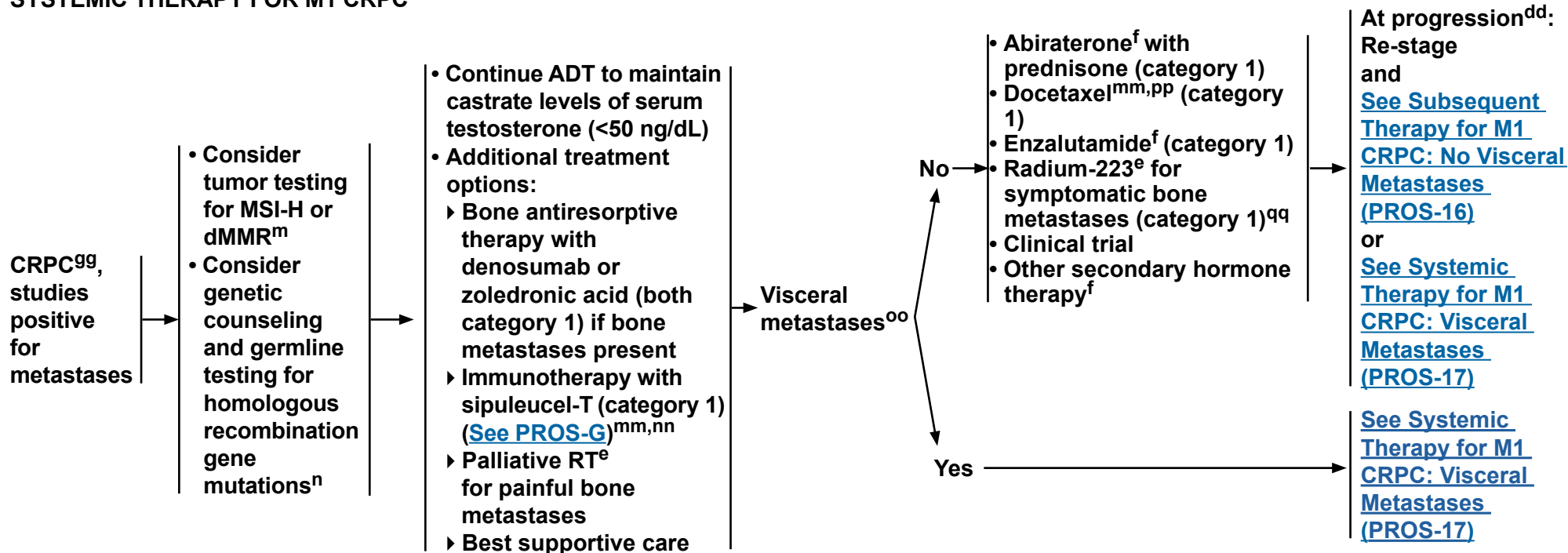
<sup>99</sup>Castration-resistant prostate cancer (CRPC) is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-1159.

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### SYSTEMIC THERAPY FOR M1 CRPC



<sup>e</sup>See [Principles of Radiation Therapy \(PROS-D\)](#).

<sup>f</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>m</sup>DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI-H or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC (see [PROS-16](#) and [PROS-17](#)).

<sup>n</sup>Consider testing for mutation in these genes (germline and somatic): *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*; refer to genetic counseling if positive. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors) <sup>dd</sup>Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See [Principles of Imaging \(PROS-B\)](#) and [Discussion](#).

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<sup>mm</sup>See [Principles of Immunotherapy and Chemotherapy \(PROS-G\)](#).

<sup>nn</sup>Sipuleucel-T has not been studied in patients with visceral metastases.

<sup>oo</sup>Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.

<sup>pp</sup>Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

<sup>qq</sup>Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See [Principles of Radiation Therapy \(PROS-D, page 2 of 3\)](#).

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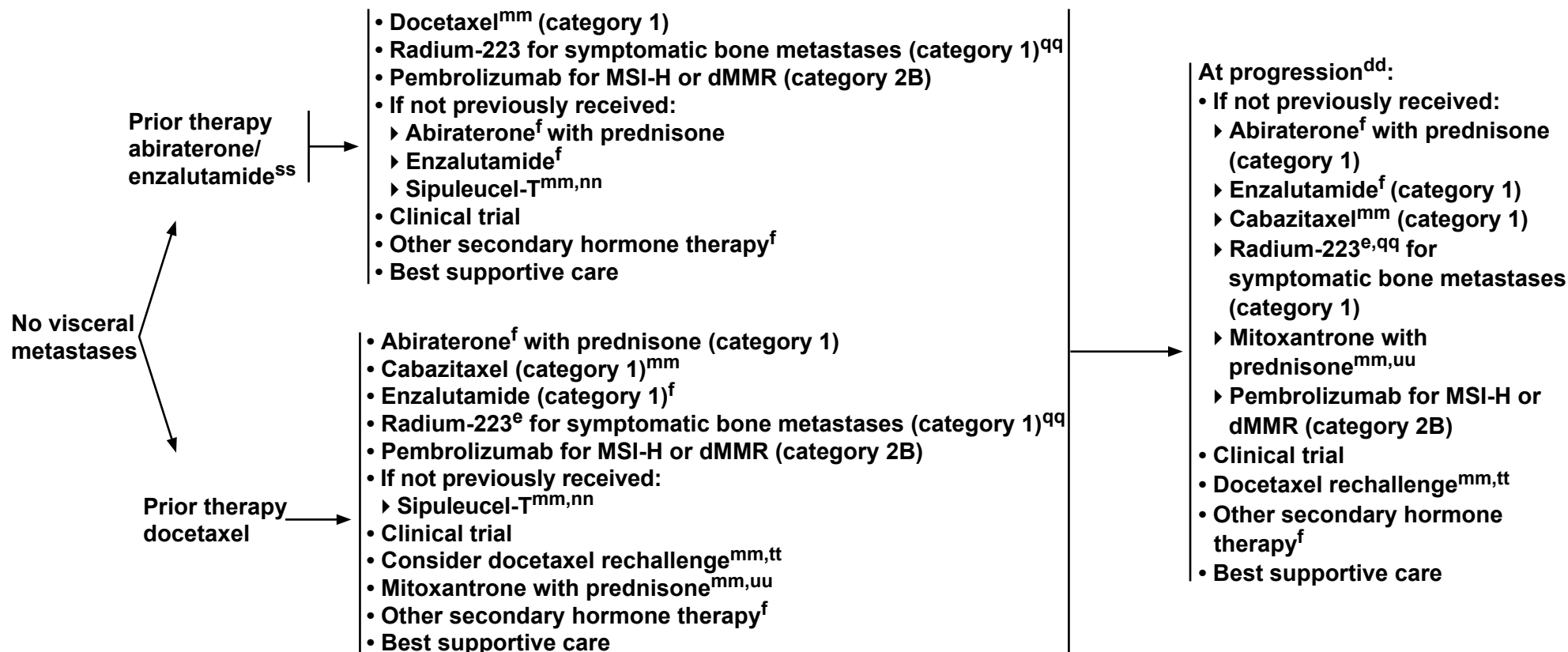
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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### SUBSEQUENT SYSTEMIC THERAPY FOR M1 CRPC<sup>rr</sup>



<sup>e</sup>See Principles of Radiation Therapy (PROS-D).

<sup>f</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>dd</sup>Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See Principles of Imaging (PROS-B) and Discussion.

<sup>mm</sup>See Principles of Immunotherapy and Chemotherapy (PROS-G).

<sup>nn</sup>Sipuleucel-T has not been studied in patients with visceral metastases.

<sup>qq</sup>Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 3).

<sup>rr</sup>Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

<sup>ss</sup>Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy (See Discussion).

<sup>tt</sup>Patients who received docetaxel with ADT in the metastatic castration-naïve setting can be considered for docetaxel rechallenge in the CRPC setting.

<sup>uu</sup>Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies.

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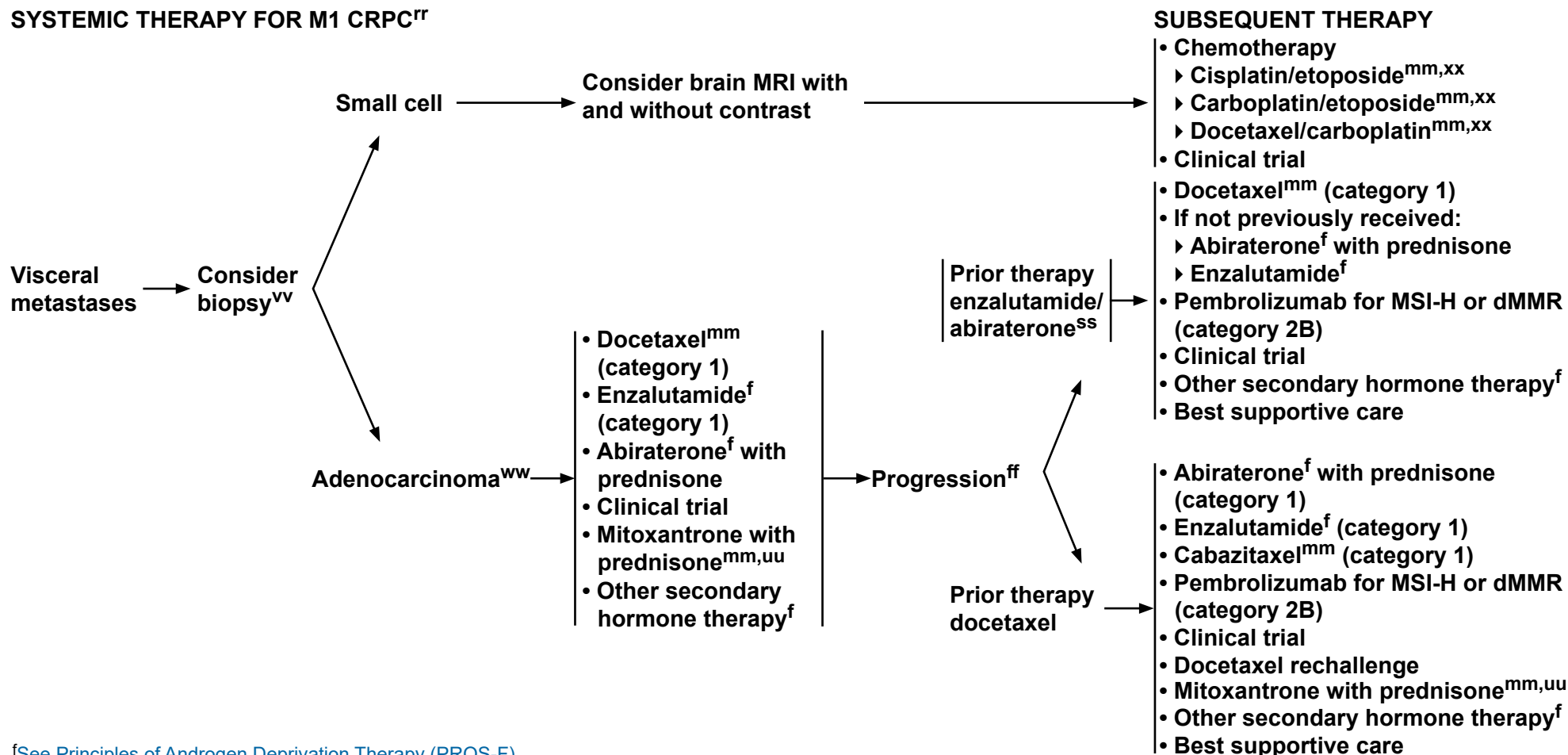




# NCCN Guidelines Version 1.2018

## Prostate Cancer

### SYSTEMIC THERAPY FOR M1 CRPC<sup>rr</sup>



<sup>f</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>dd</sup>Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See [Principles of Imaging \(PROS-B\)](#) and [Discussion](#).

<sup>mm</sup>See [Principles of Immunotherapy and Chemotherapy \(PROS-G\)](#).

<sup>rr</sup>Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

<sup>ss</sup>Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy ([See Discussion](#)).

<sup>uu</sup>Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies.

<sup>vv</sup>Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed.

<sup>ww</sup>Patients treated with first-line systemic therapy for non-visceral metastases ([see PROS-15](#)) should proceed to a different systemic therapy.

<sup>xx</sup>See [NCCN Guidelines for Small Cell Lung Cancer](#).

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables ([www.ssa.gov/OACT/STATS/table4c6.html](http://www.ssa.gov/OACT/STATS/table4c6.html)) or the WHO's Life Tables by country (<http://apps.who.int/gho/data/view.main.60000?lang=en>).
- Life expectancy can then be adjusted using the clinician's assessment of overall health as follows:
  - ▶ Best quartile of health - add 50%
  - ▶ Worst quartile of health - subtract 50%
  - ▶ Middle two quartiles of health - no adjustment
- Example of 5-year increments of age are reproduced in the [NCCN Guidelines for Older Adult Oncology](#) for life expectancy estimation.

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### PRINCIPLES OF IMAGING

#### Goals of Imaging

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in management.
- Imaging studies should be performed based on the best available clinical evidence and not influenced by business or personal interests of the care provider.
- Imaging techniques can evaluate anatomic or functional parameters.
  - ▶ Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
  - ▶ Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and spect (DWI).

#### Efficacy of Imaging

- The utility of imaging for men with early PSA persistence/recurrence after RP depends on risk group prior to operation, pathologic Gleason grade and stage, PSA, and PSA doubling time (PSADT) after recurrence. Low- and intermediate-risk groups with low serum PSAs postoperatively have a very low risk of positive bone scans or CT scans.
- Frequency of imaging should be based on individual risk, age, PSADT, Gleason score, and overall health.
- Conventional bone scans are rarely positive in asymptomatic men with PSA <10 ng/mL. The relative risk for bone metastasis or death increases as PSADT falls. Bone imaging should be performed more frequently when PSADT ≤8 mo, where there appears to be an inflection point.

#### Plain Radiography

- Plain radiography can be used to evaluate symptomatic regions in the skeleton. However, conventional plain x-rays will not detect a bone lesion until nearly 50% of the mineral content of the bone is lost or gained.
- CT or MRI may be more useful to assess fracture risk as these modalities permit more accurate assessment of cortical involvement than plain films where osteoblastic lesions may obscure cortical involvement.

#### Ultrasound

- Ultrasound uses high-frequency sound waves to image small regions of the body.
  - ▶ Standard ultrasound imaging provides anatomic information.
  - ▶ Vascular flow can be assessed using Doppler ultrasound techniques.
- Endorectal ultrasound is used to guide transrectal biopsies of the prostate.

- Endorectal ultrasound can be considered for patients with suspected recurrence after RP.
- Advanced ultrasound techniques for imaging of the prostate and for differentiation between prostate cancer and prostatitis are under evaluation.

#### Bone Imaging

- The use of the term “bone scan” refers to the conventional technetium-99m-MDP bone scan in which technetium is taken up by bone that is turning over and imaged with a gamma camera using planar imaging or 3-D imaging with single-photon emission CT (SPECT).
  - ▶ Sites of increased uptake imply accelerated bone turnover and may indicate metastatic disease.
  - ▶ Osseous metastatic disease may be diagnosed based on the overall pattern of activity, or in conjunction with anatomic imaging.
- Bone scan is indicated in the initial evaluation of patients at high risk for skeletal metastases.
- Bone scan can be considered for the evaluation of the post-prostatectomy patient when there is failure of PSA to fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more subsequent determinations.
- Bone scan can be considered for the evaluation of patients with an increasing PSA or positive DRE after RT if the patient is a candidate for additional local therapy or systemic therapy.

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### PRINCIPLES OF IMAGING

#### Bone Imaging (continued)

- Bone scans are helpful to monitor metastatic prostate cancer to determine the clinical benefit of systemic therapy. However, new lesions seen on an initial post-treatment bone scan, compared to the pre-treatment baseline scan, may not indicate disease progression.
- New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory bone scan 8–12 weeks later is warranted to determine true progression from flare reaction. Additional new lesions favor progression. Stable scans make continuation of treatment reasonable. Bone scan flare is common, particularly on initiation of new hormonal therapy, and may be observed in nearly half of patients treated with the newer agents, enzalutamide and abiraterone. Similar flare phenomena may exist with other imaging modalities, such as CT or PET/CT imaging.
- Bone scans and soft tissue imaging (CT or MRI) in men with metastatic prostate cancer or non-metastatic progressive prostate cancer may be obtained regularly during systemic therapy to assess clinical benefit.
- Bone scans should be performed for symptoms and as often as every 6–12 mo to monitor ADT. The need for soft tissue images remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable.
- PET/CT for detection of bone metastatic disease M0 CRPC
  - ▶ F-18 sodium fluoride PET/CT may be used to detect bone metastatic disease with greater sensitivity but less specificity than standard bone scan imaging.
  - ▶ Plain films, CT, MRI, or F-18 sodium fluoride PET/CT may be used after bone scan for further evaluation of equivocal findings.
  - ▶ Early detection of bone metastatic disease may result in earlier use of newer and more expensive therapies, which may not improve oncologic outcome or overall survival.

#### Computed Tomography

- CT provides a high level of anatomic detail, and may detect gross extracapsular disease, nodal metastatic disease, and/or visceral metastatic disease.
  - ▶ CT is generally not sufficient to evaluate the prostate gland.
- CT may be performed with and without oral and intravenous contrast, and CT technique should be optimized to maximize diagnostic utility while minimizing radiation dose.
- CT can be used for examination of the pelvis and/or abdomen for initial evaluation ([PROS-2](#)) and as part of workup for recurrence or progression ([see PROS-11](#) through [PROS-17](#)).

#### Magnetic Resonance Imaging

- The strengths of MRI include high soft tissue contrast and characterization, multiparametric image acquisition, multiplanar imaging capability, and advanced computational methods to assess function.
  - ▶ MRI can be performed with and without the administration of intravenous contrast material.
  - ▶ Resolution of MRI images in the pelvis can be augmented using an endorectal coil.
- Standard MRI techniques can be used for examination of the pelvis and/or abdomen for initial evaluation ([see PROS-2](#)) and as part of workup for recurrence or progression ([see PROS-11](#) through [PROS-17](#)).

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF IMAGING

#### Magnetic Resonance Imaging

- MRI may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy. MRI-US fusion biopsy may improve the detection of higher grade (Gleason score  $\geq 7$ ) cancers.
- Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer. mpMRI images are defined as images acquired with at least one more sequence in addition to the anatomical T2-weighted images, such as DWI or dynamic contrast-enhanced (DCE) images.
- mpMRI may be used to better risk stratify men who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (ie, Gleason score  $\geq 7$ ) and detect extracapsular extension (T staging). mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

#### Positron Emission Tomography/Computed Tomography (PET/CT)

- F-18 fluorodeoxyglucose (FDG) PET/CT should not be used routinely for staging prostate cancer since data are limited in patients with prostate cancer.
- The use of PET/CT or PET/MRI imaging using tracers other than F-18 FDG for staging of small volume recurrent or metastatic prostate cancer is a rapidly developing field wherein most of the data are derived from single institution series or registry studies. FDA clearance and reimbursement for some tests makes unlikely the conduct of clinical trials to evaluate their utility and impact upon oncologic outcome.
- PET/CT or PET/MRI for detection of biochemically recurrent disease.
  - C-11 choline or F-18 fluciclovine PET/CT or PET/MRI may be used to detect small volume disease in soft tissues.
  - Performance is generally poor at low PSA where pre-test probability of disease is low (PSA  $< 2.0$  ng/ml) and where salvage treatment is most likely to be beneficial.

- Histologic confirmation is recommended whenever feasible due to significant rates of false positivity.
- High variability among PET/CT or PET/MRI equipment, protocols, interpretation and institutions provides challenges for application and interpretation of the utility of PET/CT or PET/MRI.
- [Table 2 \(see Discussion\)](#) provides a summary of the main PET/CT or PET/MRI imaging tracers utilized for study in prostate cancer recurrence after operation or radiation.
- PET/CT or PET/MRI results may change treatment but may not change oncologic outcome.
  - ◊ When the worst prognosis patients from one risk group move to the higher risk group, the average outcome of both risk groups will improve even if treatment has no impact on disease. This phenomenon is known as the Will Rogers effect, in which the improved outcomes of both groups could be falsely attributed to improvement in treatment, but would be due only to improved risk group assignment. As an example, F-18 sodium fluoride PET/CT may categorize some patients as M1b who would have been categorized previously as M0 using a bone scan (stage migration). Absent any change in the effectiveness of therapy, the overall survival of both M1b and M0 groups would improve. The definition of M0 and M1 disease for randomized clinical trials that added docetaxel or abiraterone to ADT was based on CT and conventional radionuclide bone scans. Results suggest that overall survival of M1 disease is improved whereas progression-free but not overall survival of M0 disease is improved. Therefore, a subset of patients now diagnosed with M1 disease using F-18 sodium fluoride PET/CT might not benefit from the more intensive therapy used in these trials and could achieve equivalent overall survival from less intensive therapy aimed at M0 disease. Carefully designed clinical trials using proper staging will be necessary to prove therapeutic benefit, rather than making assumptions compromised by stage migration.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel ([See NCCN Guidelines for Prostate Cancer Early Detection](#)) remain concerned about over-diagnosis and over-treatment of prostate cancer. The panel recommends that patients and their physicians (ie, urologist, radiation oncologist, medical oncologist, primary care physician) consider active surveillance based on careful consideration of the patient's prostate cancer risk profile, age, and health.
- The NCCN Guidelines for Prostate Cancer distinguish between active surveillance and observation. Both involve no more often than every-6-month monitoring but active surveillance may involve surveillance prostate biopsies. Evidence of progression will prompt conversion to potentially curative treatment in active surveillance patients, whereas monitoring continues until symptoms develop or are eminent (ie, PSA >100 ng/mL) in observation patients, who will then begin palliative ADT.
- Active surveillance is preferred for men with very-low-risk prostate cancer and life expectancy ≤20 y. Observation is preferred for men with low-risk prostate cancer with life expectancy <10 y. [See Risk Group Criteria \(PROS-2\)](#).
- Patients with favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [ie, Gleason score 3 + 4 = 7], and percentage of positive biopsy cores <50 percent, and no more than one NCCN intermediate risk factor) may be considered for active surveillance. [See Discussion section](#). Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.
- Cancer progression may have occurred if:
  - Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsy.
- Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or change in exam or PSA levels that suggest symptoms are imminent.
- Patients with clinically localized prostate cancers who are candidates for definitive treatment and choose active surveillance should have regular follow-up. Follow-up should be more rigorous in younger men than in older men. Follow-up should include:
  - PSA no more often than every 6 mo unless clinically indicated
  - DRE no more often than every 12 mo unless clinically indicated
  - Needle biopsy of the prostate should be repeated within 6 mo of diagnosis if initial biopsy was <10 cores or assessment discordant (eg, palpable tumor contralateral to side of positive biopsy)
  - MRI-US fusion biopsy may improve the detection of higher grade (Gleason score ≥7) cancers.
  - A repeat prostate biopsy should be considered if prostate exam changes, MRI suggests more aggressive disease, or PSA increases, but no parameter is very reliable for detecting prostate cancer progression.
  - A repeat prostate biopsy should be considered as often as annually to assess for disease progression, because PSA kinetics may not be as reliable as monitoring parameters to determine progression of disease.
  - Repeat prostate biopsies are not indicated when life expectancy is less than 10 y or appropriate when men are on observation.
  - PSADT appears unreliable for identification of progressive disease that remains curable. Although mpMRI is not recommended for routine use, it may be considered if PSA rises and systematic prostate biopsy is negative to exclude the presence of an anterior cancer.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Advantages of active surveillance:**
  - ▶ About 2/3 of men eligible for active surveillance will avoid treatment
  - ▶ Avoidance of possible side effects of definitive therapy that may be unnecessary
  - ▶ Quality of life/normal activities potentially less affected
  - ▶ Risk of unnecessary treatment of small, indolent cancers reduced
- **Disadvantages of active surveillance:**
  - ▶ Chance of missed opportunity for cure although very low
  - ▶ About 1/3 of men will require treatment, although treatment delays do not seem to impact cure rate.
  - ▶ Periodic follow-up mpMRI and prostate biopsies may be necessary.
- **Advantages of observation:**
  - ▶ Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT
- **Disadvantages of observation:**
  - ▶ Risk of urinary retention or pathologic fracture without prior symptoms or concerning PSA level

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF RADIATION THERAPY

#### Definitive Radiation Therapy General Principles

- Highly conformal RT techniques should be used to treat localized prostate cancer.
- Photon or proton beam radiation are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles ([See Discussion](#)).
- Brachytherapy boost, when added to EBRT plus ADT in men with NCCN intermediate and high/very high risk prostate cancer, has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.
- Ideally, the accuracy of treatment should be verified by daily prostate localization, with any of the following: techniques of IGRT using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.
- Various fractionation and dose regimens can be considered depending on the clinical scenario ([See Table 1](#)). Dose escalation has been proven to achieve the best biochemical control in men with intermediate and high risk disease.
- SBRT is acceptable in practices with appropriate technology, physics and clinical expertise.
- Biologically effective dose (BED) modeling with the linear-quadratic equation may not be accurate for extremely hypofractionated (SBRT/SABR) radiation.
- For brachytherapy:
  - Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous TURP are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline in some men despite neoadjuvant ADT. Potential toxicity of ADT must be balanced against the potential benefit of target reduction.
  - Post-implant dosimetry must be performed to document the quality of the low dose-rate implant.

#### Definitive Radiation Therapy by Risk Group

- Very low risk
  - Men with NCCN very low risk prostate cancer are encouraged to pursue active surveillance.
- Low Risk
  - Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely
- Favorable Intermediate Risk
  - Prophylactic lymph node radiation is not performed routinely, and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.
- Unfavorable Intermediate Risk
  - Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered when delivering longer courses of EBRT would present medical or social hardship.
- High Risk
  - Prophylactic nodal radiation can be considered. ADT is required unless medically contraindicated. The duration of ADT may be reduced when EBRT is combined with brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered when delivering longer courses of EBRT would present a medical or social hardship.
- Very High Risk
  - Prophylactic nodal radiation should be considered. ADT is required unless medically contraindicated.
- Regional Disease
  - Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as Dose-Volume Histogram parameters allow. ADT is required unless medically contraindicated, and the addition of abiraterone and prednisone to ADT can be considered.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF RADIATION THERAPY

**Table 1: Regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms, and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.**

Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very-Low <sup>1</sup>	Low <sup>1</sup>	Favorable or good prognostic <sup>2</sup> , intermediate	Unfavorable, or poor prognostic <sup>2</sup> , intermediate	High and Very-High <sup>3</sup>	Node Positive
<b>Beam Therapies</b>						
72 Gy to 80 Gy at 2 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
75.6 Gy to 81.0 Gy at 1.8 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70.2 Gy at 2.7 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70 Gy at 2.5 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
60 Gy at 3 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
51.6 Gy at 4.3 Gy per fraction	✓	✓	✓			
37 Gy at 7.4 Gy per fraction	✓	✓	✓			
40 Gy at 8 Gy per fraction	✓	✓	✓			
36.25 Gy at 7.25 Gy per fraction	✓	✓	✓			
<b>Brachytherapy Monotherapy</b>						
Iodine 125 implant at 145 Gy	✓	✓	✓			
Palladium 103 implant at 125 Gy	✓	✓	✓			
Cesium implant at 115 Gy	✓	✓	✓			
HDR 27 Gy at 13.5 Gy in 2 implants	✓	✓	✓			
HDR 38 Gy at 9.5 Gy BID in 2 implants	✓	✓	✓			
<b>Combined EBRT and Brachytherapy (EBRT 45–50.4 Gy at 1.8–2.0 Gy/fx, unless otherwise noted)</b>						
Iodine 125 implant at 110-115 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
Palladium 103 implant at 90-100 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
Cesium implant at 85 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
HDR 21.5 Gy at 10.75 Gy x 2				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
EBRT 37.5 Gy at 2.5 Gy + 12-15 Gy single HDR				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT

<sup>1</sup>Active surveillance should be strongly considered

<sup>2</sup>"Good" or "Poor" prognostic is not strictly defined. Predictive nomograms and/or molecular testing can be used to prognosticate PSA persistence/recurrence, prostate cancer specific mortality and metastasis free survival after definitive external beam radiation therapy. Although the prognostic value has been established, the predictive value of these tests remains unknown.

<sup>3</sup>Prophylactic nodal radiation may be considered if estimate of nodal metastasis is high.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF RADIATION THERAPY

#### Salvage Brachytherapy

- Permanent LDR or temporary HDR brachytherapy is a treatment option for pathologically confirmed local recurrence after EBRT or brachytherapy. Subjects should have restaging imaging according to the NCCN high-risk stratification group to rule out regional nodal or metastatic disease. Patients should be counselled that salvage brachytherapy significantly increases the probability of urologic, sexual, and bowel toxicity compared to brachytherapy, as primary treatment previously.

#### Post-Prostatectomy Radiation Therapy

- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSADT to individualize treatment discussion. The panel recommends consultation with the American Society for Therapeutic Radiology and Oncology (ASTRO) AUA Guidelines. Evidence supports offering adjuvant/salvage RT in most men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3 disease, positive margin(s), or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and after operative side effects have improved/ stabilized. Patients with positive surgical margins may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes subsequently detectable and increases on 2 measurements or a PSA that remain persistently detectable after RP. Treatment is more effective when pre-treatment PSA is low and PSADT is long.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.
- Two years of anti-androgen therapy with 150 mg/daily of bicalutamide (RTOG 9601) or 6 months of ADT (GETUG-16) have both demonstrated improved overall and metastasis-free survival on prospective randomized trials versus radiation alone in the salvage setting.
- Nuclear medicine advanced imaging techniques can be useful for localizing disease with PSA levels as low as 0.5 ng/ml (see Discussion)
- Nomograms, and tumor based molecular assays, can be used to prognosticate risk of metastasis and prostate cancer-specific mortality in men with adverse risk features after RP.
- Target volumes include the prostate bed and may include the whole pelvis according to physician discretion.

#### Oligometastatic and Palliative Radiotherapy

- 8 Gy as a single dose is as effective for pain palliation at any bony site as longer courses of radiation, but re-treatment rates are higher.
- Widespread bone metastases can be palliated using strontium-89 or samarium-153 with or without focal external beam radiation.
- SBRT can be considered, and enrollment on clinical trials is encouraged for oligometastatic disease where durable local control is desirable.
- Treatment of the primary site in men with metastatic disease can be used to palliate obstructive symptoms due to tumor. Definitive external beam dosing regimens, or traditional palliative regimens (e.g. 30Gy/10fx or 37.5 Gy/15 fx), can be used depending on clinical scenario.

#### Radiopharmaceutical Therapy

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have castration-resistant prostate cancer (CRPC) with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease (>3 to 4 cm). Radium-223 differs from beta emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 10g/dL$ .
- Prior to subsequent doses, patients must have absolute neutrophil count  $\geq 1 \times 10^9/L$  and platelet count  $\geq 50 \times 10^9/L$  (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6-8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.
- Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except on a clinical trial.
- Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.

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### PRINCIPLES OF SURGERY

#### Pelvic Lymph Node Dissection:

- An extended PLND will discover metastases approximately twice as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases; therefore, an extended PLND is preferred when PLND is performed.
- An extended PLND includes removal of all node-bearing tissue from an area bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.
- A PLND can be excluded in patients with <2% predicated probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.
- PLND can be performed using an open, laparoscopic, or robotic technique.

#### Radical Prostatectomy:

- RP is an appropriate therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of ≥10 years, and has no serious comorbid conditions that would contraindicate an elective operation.
- High-volume surgeons in high-volume centers generally provide better outcomes.
- Laparoscopic and robot-assisted RP are used commonly. In experienced hands, the results of these approaches appear comparable to open surgical approaches.
- Blood loss can be substantial with RP, but can be reduced by careful control of the dorsal vein complex and periprostatic vessels.
- Urinary incontinence can be reduced by preservation of urethral length beyond the apex of the prostate and avoiding damage to the distal sphincter mechanism. Bladder neck preservation may decrease the risk of incontinence. Anastomotic strictures increase the risk of long-term incontinence.
- Recovery of erectile function is directly related to age at RP, preoperative erectile function, and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown to be beneficial. Early restoration of erections may improve late recovery.
- Salvage RP is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (ie, incontinence, loss of erection, anastomotic stricture) is high and the operation should be performed by surgeons who are experienced with salvage RP.

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY (ADT)

**ADT for regional disease, adjuvant treatment of lymph node metastases, or patients on observation who require treatment**

- Orchiectomy
- LHRH agonist alone
  - Goserelin, histrelin, leuprolide, or triptorelin

**Neoadjuvant, concurrent, and/or adjuvant ADT as part of radiation therapy for clinically localized disease**

- LHRH agonist alone
  - Goserelin, histrelin, leuprolide, or triptorelin
- LHRH agonist (as above) plus first-generation antiandrogen
  - Nilutamide, flutamide, or bicalutamide

**ADT for M0 or M1 castration-naïve disease:**

- Orchiectomy (for M1)
- LHRH agonist alone (first-generation antiandrogen must be given for ≥ 7 days to prevent testosterone flare if metastases are present in weight-bearing bone)
  - Goserelin, histrelin, leuprolide, or triptorelin
- LHRH agonist (as above) plus first-generation antiandrogen
  - Nilutamide, flutamide, or bicalutamide
- LHRH antagonist
  - Degarelix
- Orchiectomy, LHRH agonist, or LHRH antagonist (as above) plus abiraterone plus prednisone (for M1)

**Secondary Hormone Therapy for M0 or M1 CRPC**

- Continue LHRH agonist or antagonist to maintain castrate serum levels of testosterone (<50 ng/dL) and add:
- Second-generation antiandrogen (for M1)
  - Enzalutamide
- Androgen metabolism inhibitor (for M1)
  - Abiraterone + prednisone
- First-generation antiandrogen
  - Nilutamide, flutamide, or bicalutamide
- Ketoconazole<sup>1</sup>
- Ketoconazole plus hydrocortisone<sup>1</sup>
- Abiraterone + prednisone
- Corticosteroids (hydrocortisone, prednisone, dexamethasone)
- DES or other estrogen

<sup>1</sup>Ketoconazole ± hydrocortisone should not be used if disease progressed on abiraterone with prednisone.

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### ADT for Clinically Localized Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- ADT should not be used as monotherapy in clinically localized prostate cancer.
- Giving ADT before, during, and/or after radiation prolongs survival in selected radiation-managed patients.
- Studies of short-term (4–6 mo) and long-term (2–3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary requires further study.
- In the largest randomized trial to date using the antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes following RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.
- Many of the side effects of continuous ADT are cumulative over time on ADT.

#### ADT for PSA persistence/recurrence Without Metastases

- The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

- Some patients are candidates for salvage after PSA persistence/recurrence, which may include radiation after failed operation or RP or cryosurgery after failed radiation.
- Men with prolonged PSADTs (>12 mo) and who are older are candidates for observation.
- Men who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm. An unplanned subset analysis showed that men with Gleason sum 8–10 prostate cancer in the continuous arm had a median overall survival that was 14 mo longer (8 y) than those in the intermittent arm (6.8 y).

#### ADT for Metastatic Disease

- ADT is the gold standard for men with metastatic prostate cancer.
- A phase 3 trial compared continuous ADT to intermittent ADT, but the study could not demonstrate non-inferiority for survival. However, quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months of ADT compared to the continuous ADT arm.
- In addition, three meta-analyses of randomized controlled trials failed to show a difference in survival between intermittent and continuous ADT.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### Optimal ADT

- LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended.
- No clinical data support the use of finasteride or dutasteride with combined androgen blockade.
- Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone to effect “castration” has yet to be determined.

#### Secondary Hormone Therapy

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone should be maintained while additional therapies are applied.
- Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by imaging, M0 CRPC (non-metastatic) vs. M1 CRPC (metastatic), and whether or not the patient is symptomatic.
- In the setting in which patients have no or minimal symptoms, administration of secondary hormonal therapy including addition of, or switching to, a different anti-androgen (flutamide, bicalutamide,

nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole with or without hydrocortisone or abiraterone with prednisone), or use of an estrogen, such as DES, can be considered. Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.

- DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone (1000 mg daily on an empty stomach) and low-dose prednisone (5 mg BID) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. An improvement in overall survival was demonstrated. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
- A phase 3 study of docetaxel-naïve men showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and overall survival. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of men on enzalutamide).
- Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in men who had no or minimal symptoms due to M1 CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Both abiraterone and enzalutamide are approved in this setting and have category 1

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

recommendations. Both drugs are suitable options for men who are not good candidates to receive docetaxel.

- In the post-docetaxel CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized controlled trials. Therefore, each agent has a category 1 recommendation.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/d enzalutamide improved progression-free survival compared with 50 mg/d bicalutamide in men with treatment-naïve CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.
- Evidence-based guidance on the sequencing of these agents in either pre- or post-docetaxel remains unavailable.

#### Monitor/Surveillance

- ADT has a variety of adverse effects including hot flashes, loss of libido and erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, depression, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation ([www.nof.org](http://www.nof.org)). The National Osteoporosis Foundation guidelines include recommendations for: 1) calcium (1000-1200 mg daily from food and supplements) and vitamin D3 (400-1000 IU daily); and 2) additional treatment for men age ≥ 50y with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by DEXA and a 10-y probability of hip fracture ≥3% or a 10-y probability of a major osteoporosis-related fracture ≥20%. Fracture risk can be assessed using FRAX®, the algorithm recently released by WHO. ADT should be considered “secondary osteoporosis” when using the FRAX® algorithm. Treatment options to increase bone density, a surrogate for fracture risk in men without metastases, include denosumab (60 mg SQ every 6 mo), zoledronic acid (5

mg IV annually), and alendronate (70 mg PO weekly).

- A baseline DEXA scan should be obtained before starting therapy in men at increased risk for fracture based on FRAX® screening. A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended. The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.
- Denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from the general population.

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### PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

#### Systemic Therapy for M1 CRPC

##### • Chemotherapy

###### ▶ Docetaxel with concurrent steroid

- ◊ Concurrent steroids may include: daily prednisone or dexamethasone on the day of chemotherapy.

###### ▶ Cabazitaxel with concurrent steroid

- ◊ Concurrent steroids may include: daily prednisone or dexamethasone on the day of chemotherapy.

##### • Immunotherapy

###### ▶ Sipuleucel-T

- ◊ Only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0-1

###### ▶ Pembrolizumab (for MSI-H or dMMR)

- ◊ Only as subsequent systemic therapy for patients who have progressed through at least one line of systemic therapy for M1 CRPC

- Men with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.

- Men with high-volume, ADT-naïve, metastatic disease should be considered for ADT and docetaxel based on the results of the ECOG 3805 (CHAARTED) trial. In this study, 790 men were randomized to 6 cycles of docetaxel at 75 mg/m<sup>2</sup> every 3 weeks with dexamethasone with ADT vs. ADT alone. In the majority subset of patients with high-volume disease, defined as 4 or more bone metastases including one extra-axial bone lesion or visceral metastases, a 17-month improvement in overall survival was observed (HR 0.60; *P* = .0006). Improvements in PSA response, time to clinical progression, and time to recurrence were observed with use of docetaxel. Toxicities of 6 cycles of docetaxel included fatigue, neuropathy, stomatitis, diarrhea, and neutropenia with or without fever. The use of white cell growth factors should follow NCCN Guidelines based on risk of neutropenic fever. Docetaxel should not be offered to men without

metastatic prostate cancer or to men with low-volume metastatic prostate cancer, since this subgroup was not shown to have improved survival in either the ECOG study or a similar European (GETUG-AFU 15) trial.

- Men with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.

▶ Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 mo in the control arm to 25.8 mo in the treatment arm, which constitutes a 22% reduction in mortality risk.

▶ Sipuleucel-T is well tolerated; common complications include chills, pyrexia, and headache.

▶ Sipuleucel-T may be considered for men with CRPC who meet the following:

- ◊ Good performance status (ECOG 0-1)
- ◊ Estimated life expectancy >6 mo
- ◊ No hepatic metastases
- ◊ No or minimal symptoms

- Every-3-week docetaxel with concurrent steroid is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Abiraterone and enzalutamide have been shown to extend survival in patients who progressed on docetaxel. ([See PROS-F, 3 of 4](#)). Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival.

- Only regimens utilizing docetaxel on an every-3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m<sup>2</sup> (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel.
- Rising PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Men with mCRPC that has progressed following docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with concurrent steroid has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.
- Cabazitaxel at 20 mg/m<sup>2</sup> every 3 weeks with concurrent steroid is the standard of care in the post-docetaxel setting, with or without growth factor support. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m<sup>2</sup> every 3 weeks to 20 mg/m<sup>2</sup> every 3 weeks. Cabazitaxel 20 mg/m<sup>2</sup> had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m<sup>2</sup> had a significantly lower PSA response rate but non-significantly lower radiographic response rate and non-significantly shorter progression-free and overall survival (13.4 vs 14.5 mo) compared to 25 mg/m<sup>2</sup>. Cabazitaxel starting dose can be either 20 mg/m<sup>2</sup> or 25 mg/m<sup>2</sup> for men with mCRPC who have progressed despite prior docetaxel chemotherapy. Cabazitaxel 25 mg/m<sup>2</sup> with concurrent steroid may be considered for healthy men who wish to be more aggressive.
- Docetaxel retreatment can be attempted in men who have not demonstrated definitive evidence of progression on prior docetaxel therapy.
- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged. Several systemic agents have shown palliative and radiographic response benefits in clinical trials.
- Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
- No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens.
- [See NCCN Guidelines for Myeloid Growth Factors](#) for recommendations on growth factor support.
- In men with CRPC who have bone metastases, denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or RT to bone.
  - ▶ When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal-related events.

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

### PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- ▶ **Choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.**
  - ◊ **Zoledronic acid is given intravenously every 3 to 4 weeks. The dose is based on the serum creatinine obtained just prior to each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance <30 mL/min.**
  - ◊ **Denosumab is given subcutaneously every 4 weeks. Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance <30 mL/min. When creatinine clearance is <60 mL/min, the risk for severe hypocalcemia increases. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels.**
- ▶ **Osteonecrosis of the jaw is seen with both agents; risk is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. Patients should be referred for dental evaluation before starting either zoledronic acid or denosumab. If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s).**
- ▶ **The optimal duration of therapy for either denosumab or zoledronic acid remains uncertain.**
- ▶ **The toxicity profile of denosumab when denosumab is used in patients who have been treated with zoledronic acid remains uncertain.**
- ▶ **Clinical trials are in progress that assess a role for zoledronic acid or denosumab in men beginning ADT for bone metastases.**

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# NCCN Guidelines Version 1.2018

## Prostate Cancer

**Table 1**

**American Joint Committee on Cancer (AJCC)**  
**TNM Staging System For Prostate Cancer (8th ed., 2017)**  
**Definition of Primary Tumor (T)**

**Clinical T (cT)**

<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>T1</b>	Clinically inapparent tumor that is not palpable
<b>T1a</b>	Tumor incidental histologic finding in 5% or less of tissue resected
<b>T1b</b>	Tumor incidental histologic finding in more than 5% of tissue resected
<b>T1c</b>	Tumor identified by needle biopsy found in one or both sides, but not palpable
<b>T2</b>	Tumor is palpable and confined within prostate
<b>T2a</b>	Tumor involves one-half of one side or less
<b>T2b</b>	Tumor involves more than one-half of one side but not both sides
<b>T2c</b>	Tumor involves both sides
<b>T3</b>	Extraprostatic tumor that is not fixed or does not invade adjacent structures
<b>T3a</b>	Extraprostatic extension (unilateral or bilateral)
<b>T3b</b>	Tumor invades seminal vesicle(s)
<b>T4</b>	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

**Pathological T (pT)\*,\*\***

<b>T2</b>	Organ confined
<b>T3</b>	Extraprostatic extension
<b>T3a</b>	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck
<b>T3b</b>	Tumor invades seminal vesicle(s)
<b>T4</b>	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

\*Note: There is no pathologic T1 classification.

\*\*Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

**Definition of Regional Lymph Node (N)**

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No positive regional nodes
<b>N1</b>	Metastases in regional node(s)

**Definition of Distant Metastasis (M)\***

<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
<b>M1a</b>	Non-regional lymph node(s)
<b>M1b</b>	Bone(s)
<b>M1c</b>	Other site(s) with or without bone disease

\*Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

### AJCC PROGNOSTIC STAGE GROUPS\*

Group	T	N	M	PSA (ng/mL)	Grade Group
I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
IIB	T1-2	N0	M0	PSA <20	2
IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
IIIA	T1-2	N0	M0	PSA ≥20	1-4
IIIB	T3-4	N0	M0	Any PSA	1-4
IIIC	Any T	N0	M0	Any PSA	5
IVA	Any T	N1	M0	Any PSA	Any
IVB	Any T	Any N	M1	Any PSA	Any

\*Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

### Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell (urothelial) carcinoma of the prostate. Adjectives used to describe histologic variants of adenocarcinomas of the prostate include mucinous, signet ring cell, ductal, and neuroendocrine, including small cell carcinoma. There should be histologic confirmation of the disease.

### Definition of Histologic Grade Group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

# NCCN Guidelines Version 1.2018

## Prostate Cancer

### Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/21/17

#### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

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## Prostate Cancer

### Overview

An estimated 161,360 new cases of prostate cancer will be diagnosed in 2017, accounting for 19% of new cancer cases in men.<sup>1</sup> The age-adjusted death rates from prostate cancer have declined 51% from 1993 to 2014. Researchers have estimated prostate cancer to account for 26,730 deaths in 2017, which represent 8% of male cancer deaths.<sup>1</sup> The decreasing and comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer. The alternative hypothesis is that prostate cancer is becoming biologically less aggressive, but evidence is lacking. Early detection can lead to overtreatment of prostate cancers that do not threaten life expectancy, which results in unnecessary side effects that impair quality of life and increase health care expenditures. Over the past several years, the incidence of prostate cancer has declined, likely in part a result of decreased rates of prostate-specific antigen (PSA) screening.<sup>2-4</sup> Better use of PSA for early detection of potentially fatal prostate cancer (see the NCCN Guidelines for Prostate Cancer Early Detection, available at [www.NCCN.org](http://www.NCCN.org)) should decrease the risk of over-detection and over-treatment AND preserve the decrease in prostate cancer mortality.

### Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in prostate cancer published between September 15, 2015 and September 15, 2016, which used the search term prostate cancer, prior to the update of this version of the NCCN Guidelines® for Prostate Cancer. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>5</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 301 citations and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed relevant to these guidelines and discussed by the panel have been included in this updated Discussion section. Recommendations for which high-level evidence was lacking were based on panel review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at [www.NCCN.org](http://www.NCCN.org).

### Estimates of Life Expectancy

Estimates of life expectancy have emerged as a key determinant of primary treatment, particularly when considering active surveillance or observation. Life expectancy can be estimated for groups of men, but it is difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables, the Social Security Administration Life Insurance Tables,<sup>6</sup> or the WHO's Life Tables by Country,<sup>7</sup> and adjusted for individual patients by adding or subtracting 50% based on whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.<sup>8</sup> As an example, the Social Security Administration Life Expectancy for a 65-year-old American man is 17.7 years. If judged to be in the upper quartile of health, a life expectancy of 26.5 years is assigned. If judged to be in the lower quartile of health, a life expectancy of 8.8 years is assigned. Thus, treatment





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recommendations could change dramatically using the NCCN Guidelines if a 65-year-old man was judged to be in either poor or excellent health.

### Risk Stratification

Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is adjuvant or salvage radiation to control cancer after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by the digital rectal exam (DRE) and radiographically determined clinical T stage, Gleason score and extent of cancer in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been investigated intensively but have yet to be accepted as essential adjuncts to staging.

The NCCN Guidelines have, for many years, incorporated a risk stratification scheme that uses a minimum of stage, grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical failure after definitive local therapy.<sup>9</sup> Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.<sup>10,11</sup>

A new prostate cancer grading system was developed during the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.<sup>12</sup> Several changes were made to the assignment of Gleason pattern based on pathology (see *Gleason Grade Group Definitions* in the algorithm). The new system assigns Gleason grade groups from 1 to 5, derived from the Gleason score. Many experts believe that Gleason grade groups will enable patients to better

understand their true risk level and thereby limit overtreatment. The new Gleason grade group system was validated in 2 separate cohorts, one of >26,000 men and one of 5880 men, treated for prostate cancer with either radical prostatectomy or radiation.<sup>13,14</sup> Both studies found that Gleason grade group predicted the risk of recurrence after primary treatment. For instance, in the larger study, the 5-year biochemical recurrence-free progression probabilities after radical prostatectomy for Gleason grade groups 1 through 5 were 96% (95% CI, 95–96), 88% (95% CI, 85–89), 63% (95% CI, 61–65), 48% (95% CI, 44–52), and 26% (95% CI, 23–30), respectively. The separation between Gleason grade groups was less pronounced in the radiation therapy cohort, likely because of increased use of neoadjuvant/concurrent/adjuvant androgen deprivation therapy (ADT) in the higher risk groups. In another study of the new Gleason grade group system, all-cause mortality and prostate-cancer specific mortality were higher in men in Gleason grade group 5 than in those in Gleason grade group 4.<sup>15</sup> Additional studies have supported the validity of this new system.<sup>16-18</sup> The NCCN panel has accepted the new Gleason grade group system to inform better treatment discussions compared to those using Gleason score. Patients remain divided into very-low-, low-, intermediate-, high-, and very-high-risk groups.

The NCCN Guidelines Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed that men assigned to the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than men categorized according to Gleason score (7) or PSA level (10–20 ng/mL).<sup>19</sup> A similar trend of superior recurrence-free survival was observed in men placed in the high-risk group by clinical stage (T3a) compared to those assigned by Gleason score (8–10) or PSA level (>20 ng/mL), although it did not reach statistical significance. Other studies have reported differences in





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outcomes in the high-risk group depending on risk factors.<sup>20</sup> Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.<sup>21,22</sup>

In a retrospective study, 1024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.<sup>23</sup> Multivariate analysis revealed that primary Gleason pattern 4, percentage of positive biopsy cores  $\geq 50$ , and presence of  $>1$  intermediate-risk factors (ie, T2b-c, PSA 10-20 ng/mL, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors used these factors to separate the patients into unfavorable and favorable intermediate-risk groups and determined that the unfavorable intermediate-risk group had worse PSA recurrence-free survival and higher rates of distant metastasis and prostate cancer-specific mortality than the favorable intermediate-risk group.

### Nomograms

The more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result. A nomogram is a predictive instrument that takes a set of input data (variables) and makes predictions about an outcome. Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value. The Partin tables<sup>24-26</sup> were the first to achieve widespread use for counseling men with clinically localized prostate cancer. The tables give the probability (95% confidence intervals [CIs]) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage. Nomograms can be used to inform treatment decision-making for men contemplating active surveillance,<sup>27,28</sup> radical prostatectomy,<sup>29-32</sup> neurovascular bundle preservation<sup>33-35</sup> or omission of

pelvic lymph node dissection (PLND) during radical prostatectomy,<sup>36,37</sup> brachytherapy,<sup>29,38-40</sup> or external beam radiation therapy (EBRT).<sup>29,41</sup> Biochemical progression-free survival can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.<sup>29,42-44</sup> Potential success of adjuvant or salvage radiation therapy (RT) after unsuccessful radical prostatectomy can also be assessed using a nomogram.<sup>29,45</sup>

None of the current models predicts with perfect accuracy, and only some of these models predict metastasis<sup>28,29,42,46,47</sup> and cancer-specific death.<sup>30,32,48,49</sup> Given the competing causes of mortality, many men who sustain PSA failure will not live long enough either to develop clinical evidence of distant metastases or to die from prostate cancer. Those with a short PSA doubling time are at greatest risk of death. Not all PSA failures are clinically relevant; thus, PSA doubling time may be a more useful measure of risk of death.<sup>50</sup> Patients with a PSA nadir  $>0.5$  ng/mL after radiation and ADT have adjusted hazard ratio (HR) for all-cause mortality of 1.72 (95% CI, 1.17–2.52;  $P = .01$ ).<sup>51</sup> The NCCN Guidelines Panel recommends that NCCN risk groups be used to begin the discussion of options for the treatment of clinically localized prostate cancer and that nomograms be used to provide additional and more individualized information.

### Molecular Testing

Personalized or precision medicine is a goal for many translational and clinical investigators. The National Academy of Medicine has described several lessons that should accelerate the development of useful biomarkers<sup>52</sup> to inform men and their physicians about proper choices for treatment of clinically localized prostate cancer. Dr. Hayes has warned us that a “bad tumor marker is as bad as a bad drug.”<sup>53,54</sup> The NCCN Prostate Cancer Guidelines Panel takes pride in its leadership

regarding the need for life expectancy estimation, use of nomograms, and recommendations for active surveillance as the only option for men with low-risk prostate cancer and life expectancy less than 10 years or very-low-risk prostate cancer and life expectancy less than 20 years. Although risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about the risk of disease progression persists. American men continue to under-select active surveillance and their physicians may under-recommend it, likely as a result of this uncertainty.<sup>55</sup> In 2013, <20% of men with low-risk prostate cancer were managed with active surveillance.<sup>56</sup> However, active surveillance has become more common in some areas, such as Michigan, where its frequency has been measured and educational efforts have begun.<sup>57,58</sup>

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or radiotherapy, and likelihood of developing metastasis after operation or salvage radiotherapy.<sup>59-65</sup> No randomized controlled trials have studied the utility of these tests. Several of these assays are available, and 3 have received positive reviews by the Molecular Diagnostic Services Program (MoDX) and are likely to be covered by CMS (Centers for Medicare & Medicaid Services). Several other tests

are under development, and the use of these assays is likely to increase in the coming years.

Table 1 lists these tests in alphabetical order and provides an overview of each test, populations where each test independently predicts outcome, and supporting references. These molecular biomarker tests listed have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time. Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

### Family History and DNA Repair Mutations

Recent data indicate that men with prostate cancer may have germline mutations in 1 of 16 DNA repair genes: *BRCA2* (5%), *ATM* (2%), *CHEK2* (2%), *BRCA1* (1%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.<sup>66</sup> The overall prevalence of DNA repair gene mutations in men with metastatic or localized high-risk or low-to-intermediate-risk prostate cancer was found to be 11.8%, 6%, or 2%, respectively.<sup>66</sup> The newfound appreciation of the frequency of DNA repair gene mutations has implications for family genetic counseling, consideration for cancer risk syndromes, and better assessment of personal risk for second cancers. Some families of patients with prostate cancer may be at increased risk of breast and ovarian cancer, melanoma, pancreatic cancer (*BRCA1* and *BRCA2*), colorectal cancers (Lynch syndrome), and other cancer types.



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DNA repair gene mutations may occur at even higher frequencies (up to 25%) in metastatic castration-recurrent prostate cancer (CRPC).<sup>67</sup> Early studies suggest such mutations may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.<sup>68,69</sup> In particular, preliminary data suggest that one PARP inhibitor, olaparib, has clinical activity in such patients, and trials of this agent and other PARP inhibitors are ongoing to assess the overall net clinical benefit of such therapy for men with CRPC, particularly in those men with either germline or somatically acquired DNA repair enzyme mutations.<sup>69</sup> DNA repair defects have been reported to be predictive for sensitivity to platinum agents in other cancers.<sup>70</sup> Platinum agents have shown some activity in patients with CRPC without molecular selection.<sup>71</sup> Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed. The panel recommends clinical trial enrollment for men with prostate cancer and DNA repair gene mutations.

The panel recommends inquiring about family and personal history of cancer, with referral to genetic counseling if a familial cancer syndrome is suspected. In addition, due to the high prevalence of germline mutations, the panel recommends consideration of germline testing for all men with metastatic and high-/very-high-risk clinically localized prostate cancer; genetic counseling before and after such testing is essential.

Data also suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have increased risk of progression on local therapy and decreased OS.<sup>72-74</sup> This information should be discussed with such men if they are considering active surveillance.

### Imaging

Imaging techniques are useful for detecting metastases and tumor recurrence. Anatomic imaging techniques include radiographs,

ultrasound, CT, and MRI. Functional techniques include radionuclide bone scan (conventional Tc EDTMP scan), PET/CT, and advanced MRI, such as spectroscopy and diffusion-weighted imaging (DWI). More details on each technique are outlined under *Principles of Imaging*.

The guidelines recommend CT or MRI imaging as part of staging workup for men with longer life expectancies and T3 or T4 disease or nomogram-predicted probability of lymph node involvement >10%. Multivariate analysis of retrospective data on 643 men with newly diagnosed prostate cancer who underwent staging CT found that PSA, Gleason score, and clinical T stage were associated independently with a positive finding ( $P < .05$  for all).<sup>75</sup> Bone scans are recommended as part of staging for patients with longer life expectancies and higher Gleason grade, higher T stage, or higher PSA values as delineated in the algorithm. Retrospective evidence suggests that Gleason score and PSA levels are associated with positive bone scan findings.<sup>76</sup>

Transrectal ultrasonography (TRUS) is the most common technique for anatomic visualization of the prostate. TRUS is used to guide transrectal biopsies, and can be considered for patients with biochemical recurrence after operation or radiation.

The utility of imaging for men with an early biochemical recurrence after radical prostatectomy depends on disease risk before operation and pathologic stage, Gleason grade, PSA, and PSA doubling time after recurrence. Patients with low- and intermediate-risk disease and low postoperative serum PSA levels have a very low risk of positive bone scans or CT scans.<sup>77,78</sup> In a series of 414 bone scans performed in 230 men with biochemical recurrence after radical prostatectomy, the rate of a positive bone scan for men with PSA >10 ng/mL was only 4%.<sup>79</sup> Serial PSA measurements can be helpful for stratifying men at highest risk of progression and metastases. Some men have detectable PSA after





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radical prostatectomy due to benign prostate tissue in the prostate fossa. They have low stable PSAs and a very low risk of prostate cancer progression.<sup>80,81</sup>

The use of multiparametric MRI (mpMRI) in the staging and characterization of prostate cancer has increased in the last few years. To be considered “multi-parametric,” MRI images must be acquired with at least one more sequence apart from the anatomical T2-weighted one, such as DWIs or dynamic contrast-enhanced (DCE) images. Furthermore, a high-quality mpMRI requires a 3.0 T magnet; the need for an endorectal coil remains controversial.

Evidence supports the implementation of mpMRI in several aspects of prostate cancer management. First, mpMRI helps detect large and poorly differentiated cancers (ie, Gleason score  $\geq 7$ /Gleason grade group  $\geq 2$ ).<sup>82</sup> MpMRI has been incorporated into MRI-TRUS fusion-targeted biopsy protocols, which has led to an increase in the diagnosis of high-grade cancers with fewer biopsy cores, while reducing detection of low-grade and insignificant cancers.<sup>83-85</sup> Second, mpMRI aids in the detection of extracapsular extension (T staging), with high negative predictive values in low-risk men.<sup>86</sup> MpMRI results may inform decision-making regarding nerve-sparing operation.<sup>87</sup> Third, mpMRI has been shown to be equivalent to CT scan for staging of pelvic lymph nodes.<sup>88,89</sup> Finally, mpMRI out-performs bone scan and targeted x-rays for detection of bone metastases, with a sensitivity of 98% to 100% and specificity of 98% to 100% (vs. sensitivity of 86% and specificity of 98%–100% for bone scan plus targeted x-rays).<sup>90</sup>

C-11 choline PET/CT has been used to detect and differentiate prostate cancer from benign tissue.<sup>91,92</sup> The sensitivity and specificity of the technique in restaging patients with biochemical failure were 85% and

88%, respectively.<sup>93</sup> C-11 choline PET/CT may be useful to detect distant metastases in these patients.

### Risks of Imaging

As with any medical procedure, imaging is not without risk. Some of these risks are concrete and tangible, while others are less clear. Risks associated with imaging include exposure to ionizing radiation, adverse reaction to contrast media, false-positive scans, and over-detection.

Deterministic and stochastic are two types of effects from exposure to ionizing radiation by x-ray, CT, or PET/CT. Deterministic effects are those that occur at a certain dose level, and include events such as cataracts and radiation burns. No effect is seen below the dose threshold. Medical imaging is always performed almost below the threshold for deterministic effects. Stochastic effects tend to occur late, increase in likelihood as dose increases, and have no known lower “safe” limit. The major stochastic effect of concern in medical imaging is radiation-induced malignancy. Unfortunately, no direct measurements are available to determine risk of cancer arising from one or more medical imaging events, so risks are calculated using other models (such as from atomic bomb survivors). The literature is conflicting with regards to the precise risk of secondary malignancies in patients undergoing medical imaging procedures. There is a small but finite risk of developing secondary malignancies as a result of medical imaging procedures, and the risk is greatest in young patients. However, the absolute risk of fatal malignancy arising from a medical imaging procedure is very low, and is difficult to detect given the prevalence of cancer in the population and the multiple factors that contribute to oncogenesis.<sup>94</sup> Efforts should be made to minimize dose from these procedures, which begin with judicious use of imaging only when



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justified by the clinical situation. Harm may arise from not imaging a patient, through disease non-detection or erroneous staging.

Many imaging studies make use of contrast material delivered by oral, intravenous, or rectal routes. The use of contrast material may improve study performance, but reactions to contrast material may occur and they should be used only when warranted. Some patients develop adverse reactions to iodinated intravenous contrast material. Most reactions are mild cutaneous reactions (eg, hives, itching) but occasionally severe reactions can be life-threatening (bronchospasm or anaphylactoid). The risk of severe reaction is low with non-ionic contrast materials and may be about 1:170,000 injections.<sup>95</sup> Both iodinated CT contrast material and gadolinium-based MR contrast materials can affect renal function, particularly when renal function is impaired. MR contrast materials also have been associated with systemic nephrogenic sclerosis in patients with impaired renal function. Centers performing imaging studies with contrast materials should have policies in place to address the use of contrast in these patients.

Every imaging test has limitations for sensitivity, specificity, and accuracy, which are modulated further by the expertise of the interpreting physician. Harm can arise from failure to detect a tumor or tumor recurrence (ie, false negative), but harm to the patient and added expense to the medical system also can result from false-positive scans. Improper interpretation of a benign finding as malignant can lead to significant patient anxiety, additional and unnecessary imaging, and invasive procedures that carry their own risks for adverse outcomes.

Accurate and medically relevant interpretation of imaging studies requires familiarity and expertise in the imaging modality, attention to detail in image review, knowledge of tumor biology, and familiarity with treatment options and algorithms. Challenging cases are best

addressed through direct communication, either physician-to-physician or in a multidisciplinary tumor board setting.

Medical imaging is a critical tool in the evaluation and management of patients with malignancy. However, as with any medical procedure, imaging is not without risks to patients. Inappropriate use of imaging also has been identified as a significant contributor to health care costs in the United States and worldwide. Therefore, imaging should be performed only when medically appropriate, and in a manner that reduces risk (eg, minimizing radiation dose). An algorithmic approach to the use of imaging, such as by NCCN and the Appropriateness Criteria developed by the American College of Radiology,<sup>96</sup> can assist medical decision-making.

### Observation

Observation involves monitoring the course of prostate cancer with the expectation to deliver palliative therapy for development of symptoms or change in exam or PSA that suggests symptoms are imminent. Observation thus differs from active surveillance. The goal of observation is to maintain quality of life by avoiding noncurative treatment when prostate cancer is unlikely to cause mortality or significant morbidity. The main advantage of observation is avoidance of possible side effects of unnecessary definitive therapy or ADT. However, patients may develop urinary retention or pathologic fracture without prior symptoms or increasing PSA level.

Observation is applicable to elderly or frail men with comorbidity that will likely out-compete prostate cancer. Johansson and colleagues<sup>97</sup> observed that only 13% of men developed metastases 15 years after diagnosis of T0-T2 disease and only 11% had died from prostate cancer. Since prostate cancer will not be treated for cure for patients with shorter life expectancies, observation for as long as possible is a

reasonable option based on physician's discretion. Monitoring should include PSA and DRE no more often than every 6 months, but will not involve surveillance biopsies. When symptoms develop or are imminent, patients can begin palliative ADT.

### Active Surveillance

Active surveillance (also referred to as watchful waiting, expectant management, or deferred treatment) involves actively monitoring the course of the disease with the expectation to deliver curative therapy if the cancer progresses. Unlike observation, active surveillance is mainly applicable to younger men with seemingly indolent cancer with the goal to defer treatment and its potential side effects. Because these patients have a longer life expectancy, they should be followed closely and treatment should start promptly should the cancer progress so as not to miss the chance for cure.

In one study, approximately two thirds of eligible men avoided treatment, and thus the possible associated side effects of treatment, after 5 years of active surveillance.<sup>98</sup> In another study, 55% of the population remained untreated at 15 years.<sup>99</sup> Although a proportion of men will eventually undergo treatment, the delay does not appear to impact cure rates, and several studies have shown active surveillance is safe.<sup>98-102</sup> In fact, a 2015 meta-analysis of 26 active surveillance cohort studies that included 7627 men identified only 8 prostate cancer deaths and 5 cases of metastasis.<sup>103</sup> Further, the ProtecT study, which randomized 1643 men with localized prostate cancer to active surveillance, radical prostatectomy, or radiation therapy, found no significant difference in the primary outcome of prostate cancer mortality at a median of 10 years follow-up.<sup>104</sup> Of 17 prostate cancer deaths (1% of study participants), 8 were in the active surveillance group, 5 were in the operation group, and 4 were in the radiation group ( $P = .48$  for the

overall comparison). However, higher rates of disease progression and metastases were seen in the active surveillance group. Approximately 23% of participants had Gleason scores 7–10, and 5 of 8 deaths in the active surveillance group were in this subset. Patient-reported outcomes were compared among the three groups.<sup>105</sup> The operation group experienced the greatest negative effect on sexual function and urinary continence, whereas bowel function was worst in the radiation group.

In addition, studies have shown that active surveillance does not adversely impact psychologic well-being or quality of life.<sup>105-110</sup> Possible disadvantages of active surveillance are listed in the *Principles* section of these guidelines and include the possible necessity of follow-up prostate biopsies.

### Rationale

The NCCN Guidelines Panel remains concerned about the problems of over-treatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA for early detection or screening (see [NCCN Guidelines for Prostate Cancer Early Detection](#)).

The debate about the need to diagnose and treat every man who has prostate cancer is fueled by the high prevalence of prostate cancer upon autopsy of the prostate<sup>111</sup>; the high frequency of positive prostate biopsies in men with normal DREs and serum PSA values<sup>112</sup>; the contrast between the incidence and mortality rates of prostate cancer; and the need to treat an estimated 37 men with screen-detected prostate cancer<sup>113,114</sup> or 100 men with low-risk prostate cancer<sup>115</sup> to prevent one death from the disease. The controversy regarding over-treatment of prostate cancer and the value of prostate cancer early detection<sup>113-119</sup> has been informed further by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC).<sup>120,121</sup> Many believe that this study best





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approximates proper use of PSA for early detection since it was population-based and involved a 1:1 randomization of 20,000 men who received PSA every 2 years and used thresholds for prostate biopsy of PSA >3, and >2.5 since 2005. The follow-up of 14 years is longer than the European study as a whole (9 years) and Prostate, Lung, Colorectal, and Ovarian (PLCO) (11.5 years). Prostate cancer was diagnosed in 12.7% of the screened group compared to 8.2% of the control group. Prostate cancer mortality was 0.5% in the screened group and 0.9% in the control group, which gave a 40% absolute cumulative risk reduction of prostate cancer death (compared to ERSPC 20% and PLCO 0%).<sup>120</sup> Most impressively, 40% of the patients were managed initially using active surveillance and 28% were still on active surveillance at the time these results were analyzed. To prevent a prostate cancer death, 12 men would need to be diagnosed and treated as opposed to the ERSPC as a whole where 37 men needed to be treated. Thus, early detection, when applied properly, should reduce prostate cancer mortality. However, that reduction comes at the expense of over-treatment that may occur in as many as 50% of men treated for PSA-detected prostate cancer.<sup>122</sup>

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers were overtreated<sup>123</sup> and that PSA detection was responsible for up to 12.3 years of lead-time bias.<sup>124</sup> The NCCN Guidelines Panel responded to these evolving data with careful consideration of which men should be recommended active surveillance. However, the NCCN Guidelines Panel recognizes the uncertainty associated with the estimation of chance of competing causes of death, the definition of very-low- or low-risk prostate cancer, the ability to detect disease progression without compromising chance of cure, and the chance and consequences of treatment side effects.

### Application

Epstein and colleagues<sup>125</sup> introduced clinical criteria to predict pathologically “insignificant” prostate cancer. Insignificant prostate cancer is identified by: clinical stage T1c, biopsy Gleason score ≤6/Gleason grade group I, the presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these as the sole decision maker. Studies have shown that as many as 8% of cancers that qualified as insignificant using the Epstein criteria were not organ-confined based on postoperative findings.<sup>126,127</sup> A new nomogram may be better.<sup>128</sup> Although many variations upon this definition have been proposed (reviewed by Bastian and colleagues<sup>129</sup>), a consensus of the NCCN Guidelines Panel was reached that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to men with life expectancy less than 20 years. The confidence that Americans with very-low-risk prostate cancer have a very small risk of prostate cancer death is enhanced by lead time bias introduced by PSA early detection that ranges from an estimated 12.3 years in a 55-year-old man to 6 years in a 75-year-old man.<sup>124</sup>

The role for active surveillance should increase with the shift towards earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly due to heterogeneity of the patient populations (reviewed by Sanda and Kaplan<sup>130</sup>). Ultimately, a recommendation for active surveillance must be based on careful individualized weighing of a number of factors: life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference.



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Race is emerging as another important factor to consider, particularly for African-American men. From 2010 to 2012, African-American men had a higher lifetime risk of developing (18.2% vs. 13.3%) and dying from (4.4% vs 2.4%) prostate cancer compared with Caucasian-American men.<sup>131</sup> Multiple studies have shown that African Americans with very-low-risk prostate cancer may harbor high-grade (Gleason sum  $\geq 7$ ) cancer that is not detected by pre-treatment biopsies. Compared to Caucasian Americans matched on clinical parameters, African Americans have been reported to have 1.7- to 2.3-fold higher change of pathologic upgrading.<sup>132,133</sup> Several studies have reported that, among men with low-risk prostate cancer who are enrolled in active surveillance programs, African Americans have higher risk of disease progression to higher Gleason grade or volume cancer than Caucasian Americans.<sup>134-136</sup> African Americans in the low- to intermediate-risk categories also appear to suffer from an increased risk of biochemical recurrence after treatment.<sup>137</sup> In addition, African American men with low-risk or favorable intermediate-risk prostate cancer have an increase in all-cause mortality after treatment, mainly due to cardiovascular complications after ADT.<sup>138</sup> Reasons for these clinical disparities are under investigation and may include difference in tumor location within the prostate that may reflect different prostate cancer subtypes related to differences in gene expression.<sup>139-142</sup> In addition, access to health care may play a significant role, because in a retrospective study of 895 men in the SEARCH database, no significant differences were seen in the rates of pathological upgrading, up-staging, or biochemical recurrence between African American and Caucasian Americans.<sup>143</sup> Strategies to improve risk-stratification for African Americans considering active surveillance may include mpMRI in concert with targeted image-guided biopsies, which has been reported to improve detection of clinically significant tumors in some men.<sup>144</sup>

### Surveillance Program and Reclassification Criteria

Each of the major active surveillance series has used different criteria for reclassification.<sup>99,101,145-149</sup> Reclassification criteria were met by 23% of men with a median follow-up of 7 years in the Toronto experience,<sup>147</sup> 36% of men with a median follow-up of 5 years in the Johns Hopkins experience,<sup>101</sup> and 16% of men with a median follow-up of 3.5 years in the University of California, San Francisco (UCSF) experience<sup>146</sup> (Table 2). Uncertainty regarding reclassification criteria and the desire to avoid missing an opportunity for cure have driven several reports in the past year that have dealt with the validity of commonly used reclassification criteria. The Toronto group demonstrated that a PSA trigger point of PSA doubling time  $< 3$  years could not be improved upon by using a PSA threshold of 10 or 20, PSA doubling time calculated in various ways, or PSA velocity  $> 2$  ng/mL/y.<sup>150</sup> The Johns Hopkins group used biopsy-demonstrated reclassification to Gleason pattern 4 or 5 or increased tumor volume on biopsy as their criteria for reclassification. Of 290 men on an annual prostate biopsy program, 35% demonstrated reclassification at a median follow-up of 2.9 years.<sup>151</sup> Neither PSA doubling time (area under the curve [AUC], 0.59) nor PSA velocity (AUC 0.61) was associated with prostate biopsy reclassification. Both groups have concluded that PSA kinetics cannot replace regular prostate biopsy, although treatment of most men who demonstrate reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival.

Early experience supports the utilization of mpMRI in biopsy protocols to better risk-stratify men under active surveillance.<sup>152-154</sup> However, more recent studies have shown that a significant proportion of high-grade cancers are detected with systematic biopsy and not targeted biopsy in men on active surveillance.<sup>155-157</sup>



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A repeat prostate biopsy should be considered if prostate exam changes, if mpMRI (if done) suggests more aggressive disease, or if PSA increases, but no parameter is very reliable for detecting prostate cancer progression. Repeat biopsy is useful to determine whether higher Gleason grade elements, which may influence prognosis and hence the decision to continue active surveillance or to proceed to definitive local therapy, are evolving although the risk appears small.<sup>158</sup> Treatment of all men who developed Gleason pattern 4 on annual prostate biopsies has thus far resulted in only 2 prostate cancer deaths among 1298 men (0.15%) in the Johns Hopkins study.<sup>101</sup> However, it remains uncertain whether treatment of all who progress to Gleason pattern 4 was necessary. Studies remain in progress to identify the best trigger points when interventions with curative intent may still be successful.

The Toronto group published on 3 patients who died of prostate cancer in their experience with 450 men.<sup>147</sup> These 3 deaths led them to revise their criteria for offering men active surveillance, because each of these 3 men probably had metastatic disease at the time of entry on active surveillance. In 450 men followed for a median of 6.8 years, overall survival was 78.6% and prostate cancer-specific survival was 97.2%.<sup>147</sup> Of the 30% (n = 145) of men who progressed, 8% had an increase in Gleason grade, 14% had PSA doubling time <3 years, 1% developed a prostate nodule, and 3% were treated because of anxiety. One hundred thirty-five of these 145 men were treated: 35 by radical prostatectomy, 90 by EBRT with or without ADT, and 10 with ADT alone. Follow-up is available for 110 of these men, and 5-year biochemical progression-free survival is 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation. Longer-term follow-up of this cohort was reported in 2015.<sup>99</sup> The 10- and 15-year actuarial cause-specific survival rates for the entire cohort were 98.1% and 94.3 %, respectively. Only 15

of 993 (1.5%) patients had died of prostate cancer, an additional 13 men (1.3%) had developed metastatic disease, and only 36.5% of the cohort had received treatment by 10 years. In an analysis of 592 patients enrolled in this cohort who had ≥1 repeat prostate biopsy, 31.3% of cases were upgraded. Fifteen percent of upgraded cases were upgraded to Gleason ≥8, and 62% of total upgraded cases proceeded to active treatment.<sup>159</sup> Another analysis of this cohort revealed that metastatic disease developed in 13 of 133 men with Gleason 7 disease (9.8%) and 17 of 847 men with Gleason ≤6 disease (2.0%).<sup>160</sup> PSA doubling time and the number of positive scores were also predictors of increased risk for the development of metastatic disease.

In comparison, among 192 men on active surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience, 5-year biochemical progression-free survival was 96% for those who underwent radical prostatectomy and 75% for those who underwent radiation.<sup>149</sup> The two groups were similar by pathologic Gleason grade, pathologic stage, and margin positivity. All men treated by radical prostatectomy after progression on active surveillance had freedom from biochemical progression at median follow-up of 37.5 months, compared to 97% of men in the primary radical prostatectomy group at median follow-up of 35.5 months. A later publication from this group showed that 23 of 287 men who were treated after active surveillance (8%) experienced biochemical recurrence, and the rate was independent of the type of treatment.<sup>101</sup> Several studies have shown that delayed radical prostatectomy does not increase the rates of adverse pathology.<sup>161-164</sup>

The panel believes there is an urgent need for further clinical research regarding the criteria for recommending active surveillance, the criteria for reclassification on active surveillance, and the schedule for active





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surveillance especially as it pertains to prostate biopsies, which pose an increasing burden. One such study is a prospective multiinstitutional cohort study, which has been funded by the NCI.<sup>163</sup> Nine hundred and five men, median age 63 and median follow-up 28 months, demonstrated 19% conversion to therapy. Much should be learned about the criteria for selection of and progression on active surveillance as this cohort and research effort mature. Literature suggests that as many as 7% of men undergoing prostate biopsy will suffer an adverse event,<sup>117</sup> and those who develop urinary tract infection are often fluoroquinolone-resistant.<sup>165</sup> Radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.<sup>166</sup>

### Radical Prostatectomy

Radical prostatectomy is appropriate for any patient whose cancer appears clinically localized to the prostate. However, because of potential perioperative morbidity, radical prostatectomy should be reserved for patients whose life expectancy is 10 years or more. Stephenson and colleagues<sup>32</sup> reported a low 15-year prostate cancer-specific mortality of 12% in patients who underwent radical prostatectomy (5% for patients with low-risk disease), although it is unclear whether the favorable prognosis is due to the effectiveness of the procedure or the low lethality of cancers detected in the PSA era.

Radical prostatectomy was compared to watchful waiting in a randomized trial of 695 patients with early-stage prostate cancer (mostly T2).<sup>167,168</sup> With a median follow-up of 12.8 years, those assigned to the radical prostatectomy group had significant improvements in disease-specific survival, overall survival, and risk of metastasis and local progression.<sup>167</sup> The reduction in mortality was confirmed at 23 years of follow-up, with an absolute difference of 11%.<sup>168</sup> Overall, 8 men needed

to be treated to avert one death; that number fell to 4 for men younger than 65 years of age. The results of this trial offer high-quality evidence to support radical prostatectomy as a treatment option for clinically localized prostate cancer.

Some patients at high or very high risk may benefit from radical prostatectomy. In an analysis of 842 men with Gleason scores 8 to 10 at biopsy who underwent radical prostatectomy, predictors of unfavorable outcome included PSA level over 10 ng/mL, clinical stage T2b or higher, Gleason score 9 or 10, higher number of biopsy cores with high-grade cancer, and over 50% core involvement.<sup>169</sup> Patients without these characteristics showed higher 10-year biochemical-free and disease-specific survival after radical prostatectomy compared to those with unfavorable findings (31% vs. 4% and 75% vs. 52%, respectively). Radical prostatectomy is an option for men with high-risk disease and in select patients with very high-risk disease.

Radical prostatectomy is a salvage option for patients experiencing biochemical recurrence after primary EBRT, but morbidity (incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.<sup>170,171</sup> Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.<sup>170</sup> Patient selection is important, and salvage prostatectomy should only be performed by highly experienced surgeons.

### Operative Techniques and Adverse Effects

Long-term cancer control has been achieved in most patients with both the retropubic and the perineal approaches to radical prostatectomy; high-volume surgeons in high-volume centers generally achieve superior outcomes.<sup>172,173</sup> Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to



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conventional approaches in experienced hands.<sup>174,175</sup> In a cohort study using U.S. Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data on 8837 patients, minimally invasive compared to open radical prostatectomy was associated with shorter length of hospital stay, less need for blood transfusions, and fewer surgical complications, but rates of incontinence and erectile dysfunction were higher.<sup>176</sup> A second large study reported no difference in overall complications, readmission, and additional cancer therapies between open and robot-assisted radical prostatectomy, although the robotic approach was associated with higher rates of genitourinary complications and lower rates of blood transfusion.<sup>177</sup> Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies<sup>176</sup> or rate of positive surgical margins,<sup>178</sup> although longer follow-up is necessary. A meta-analysis on 19 observational studies (n = 3893) reported less blood loss and lower transfusion rates with minimally invasive techniques than with open operation.<sup>178</sup> Risk of positive surgical margins was the same. Two more recent meta-analyses showed a statistically significant advantage in favor of a robotic approach compared to an open approach in 12-month urinary continence<sup>179</sup> and potency recovery.<sup>180</sup> Early results from a randomized controlled phase 3 study comparing robot-assisted laparoscopic radical prostatectomy and open radical retropubic prostatectomy in 326 men were published in 2016.<sup>181</sup> Urinary function and sexual function scores and rates of postoperative complications did not differ significantly between the groups. Rates of positive surgical margins were similar, based on a superiority test (10% in the open group vs. 15% in the robotic group). Longer follow-up of this trial is needed to assess differences in more relevant oncologic outcomes.

An analysis of the Prostate Cancer Outcomes Study on 1655 men with localized prostate cancer compared long-term functional outcomes after

radical prostatectomy or EBRT.<sup>182</sup> At 2 and 5 years, patients who underwent radical prostatectomy reported higher rates of urinary incontinence and erectile dysfunction but lower rates of bowel urgency. However, no significant difference was observed at 15 years. In a large retrospective cohort study involving 32,465 patients, those who received EBRT had a lower 5-year incidence of urological procedures than those who underwent radical prostatectomy, but higher incidence for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies.<sup>183</sup>

Return of urinary continence after radical prostatectomy may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Bladder neck preservation may allow more rapid recovery of urinary control.<sup>184</sup> Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary function was reported with nerve-sparing techniques.<sup>185</sup> Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.<sup>186</sup> The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.<sup>87</sup>

### Pelvic Lymph Node Dissection

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Guidelines Panel chose 2% as the cutoff for PLND since this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.<sup>37</sup> A more recent analysis of 26,713 patients in the SEER database treated with radical prostatectomy and PLND between 2010 and 2013 found that the 2% nomogram threshold





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would avoid 22.3% of PLNDs at a cost of missing 3.0% of positive pelvic lymph nodes.<sup>187</sup> The panel recommends use of a nomogram developed at Memorial Sloan Kettering Cancer Center that uses pretreatment PSA, clinical stage, and Gleason sum to predict the risk of pelvic lymph node metastases.<sup>37</sup>

PLND should be performed using an extended technique.<sup>188,189</sup> An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. Removal of more lymph nodes using the extended technique has been associated with increased likelihood of finding lymph node metastases, thereby providing more complete staging.<sup>190-192</sup> A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases,<sup>191,193-195</sup> although definitive proof of oncologic benefit is lacking.<sup>196</sup> PLND can be performed safely laparoscopically, robotically, or as an open procedure, and complication rates should be similar among the three approaches.

## Radiation Therapy

### External Beam Radiation Therapy

Over the past several decades, RT techniques have evolved to allow higher doses of radiation to be administered safely. Three-dimensional (3D) conformal radiation therapy (3D-CRT) uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows higher cumulative doses to be delivered with lower risk of late effects.<sup>46,197-199</sup> The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), is used increasingly in practice<sup>200</sup> because IMRT reduced the risk of gastrointestinal toxicities

and rates of salvage therapy compared to 3D-CRT in some but not all studies, although treatment cost is increased.<sup>201-204</sup>

Daily prostate localization using image-guided radiation therapy (IGRT) is essential with either 3D-CRT or IMRT for target margin reduction and treatment accuracy. Imaging techniques, such as ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can improve cure rates and decrease complications.

These techniques have permitted safer dose escalation, and results of randomized trials have suggested that dose escalation is associated with improved biochemical outcomes.<sup>205-210</sup> Kuban and colleagues<sup>208</sup> published an analysis of their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. Freedom from biochemical or clinical failure was higher in the group randomized to 78 Gy compared to 70 Gy (78% vs. 59%,  $P = .004$ ) at a median follow-up of 8.7 years. The difference was even greater among patients with diagnostic PSA >10 ng/mL (78% vs. 39%,  $P = .001$ ). An analysis of the National Cancer Data Base found that dose escalation (75.6–90 Gy) resulted in a dose-dependent improvement in overall survival for men with intermediate- or high-risk prostate cancer.<sup>211</sup> In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses up to 81.0 Gy.<sup>201,212,213</sup>

Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and their efficacy has been similar or non-inferior to conventionally fractionated IMRT.<sup>214-218</sup> Toxicity was similar between moderately hypofractionated and conventional regimens in many,<sup>214,215,217</sup> but not all



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of the trials.<sup>218,219</sup> These RT techniques can be considered as an alternative to conventionally fractionated regimens when clinically indicated.

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.<sup>220</sup> EBRT of the primary prostate cancer shows several distinct advantages over radical prostatectomy. EBRT avoids complications associated with operation, such as bleeding and transfusion-related effects, and risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-CRT and IMRT techniques are available widely and are possible for patients over a wide range of ages. EBRT has a low risk of urinary incontinence and stricture and a good chance of short-term preservation of erectile function.<sup>221</sup>

The disadvantages of EBRT include a treatment course of 8 to 9 weeks. Up to 50% of patients have some temporary bladder or bowel symptoms during treatment. There is a low but definite risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time.<sup>221,222</sup> Some new data suggest that rectal complications may be reduced using biomaterials placed to increase the distance between the rectum and the prostate that degrade after treatment is complete.<sup>223</sup> If the cancer recurs, salvage radical prostatectomy is associated with a higher risk of complications than primary radical prostatectomy.<sup>224</sup> Contraindications to EBRT include prior pelvic irradiation, active inflammatory disease of the rectum, or a permanent indwelling Foley catheter. Relative contraindications include very low bladder capacity, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

### **EBRT for Early Disease**

EBRT is one of the principal treatment options for clinically localized prostate cancer. The NCCN Guidelines Panel consensus was that modern EBRT and surgical series show similar progression-free survival in patients with low-risk disease treated with radical prostatectomy or EBRT. In a study of 3546 patients treated with brachytherapy plus EBRT, disease-free survival remained steady at 73% between 15 and 25 years of follow-up.<sup>225</sup>

### **EBRT for Patients with High-Risk or Very-High-Risk Disease**

EBRT has demonstrated efficacy in patients at high risk and very high risk. One study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT.<sup>226</sup> In another study (RTOG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse.<sup>227</sup> Two other randomized phase 3 trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease.<sup>228-231</sup> In all four studies, the combination group showed improved disease-specific and overall survival compared to single-modality treatment.

### **EBRT for Node-positive Disease**

See *Adjuvant or Salvage Therapy after Radical Prostatectomy* under *NCCN Recommendations*.

### **Stereotactic Body Radiotherapy**

The relatively slow proliferation rate of prostate cancer is reflected in a low  $\alpha/\beta$  ratio,<sup>232</sup> most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Since the  $\alpha/\beta$  ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with radiation, appropriately designed radiation treatment fields and schedules using extremely



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hypofractionated regimens should result in similar cancer control rates without increased risk of late toxicity.

Stereotactic body radiotherapy (SBRT) is a technique that delivers highly conformal, high-dose radiation in 5 or fewer treatment fractions, which are safe to administer only with precise, image-guided delivery.<sup>233</sup> Single institution series with median follow-up as long as 6 years report excellent biochemical progression-free survival and similar early toxicity (bladder, rectal, and quality of life) compared to standard radiation techniques.<sup>232-238</sup> According to a pooled analysis of phase 2 trials, the 5-year biochemical relapse-free survival is 95%, 84%, and 81% for patients with low-, intermediate-, and high-risk disease, respectively.<sup>239</sup>

SBRT may be associated with more toxicity than moderately fractionated IMRT. One retrospective study of 4005 patients reported higher genitourinary toxicity at 24 months after SBRT than IMRT (44% vs. 36%;  $P = .001$ ).<sup>240</sup> Another phase 2 trial found increased toxicity with doses >47.5 Gy delivered in five fractions.<sup>241</sup> An analysis using the SEER database also reported that SBRT was more toxic than IMRT.<sup>242</sup>

SBRT/extremely hypofractionated image-guided IMRT regimens (6.5 Gy per fraction or greater) can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise. Longer follow-up and prospective multiinstitutional data are required to evaluate longer-term results, especially since late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8–2.0 Gy per fraction).

### Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.<sup>11,243</sup>

However, increasing evidence suggests that technical advancements in brachytherapy may provide a role for contemporary brachytherapy in high-risk localized and locally advanced prostate cancer.<sup>244,245</sup>

Brachytherapy involves placing radioactive sources into the prostate tissue. There are currently two methods for prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR).

### LDR Brachytherapy

LDR brachytherapy consists of placement of permanent seed implants in the prostate. The short range of the radiation emitted from these low-energy sources allows delivery of adequate dose levels to the cancer within the prostate, with excessive irradiation of the bladder and rectum avoided. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution.

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to radical prostatectomy (over 90%) for low-risk prostate cancer with medium-term follow-up.<sup>246</sup> In addition, the risk of incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short term.<sup>222</sup> Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years. IMRT causes less acute and late genitourinary toxicity and similar freedom from biochemical failure compared with iodine-125 or palladium-103 permanent seed implants.<sup>247,248</sup>



Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers (cT1c–T2a, Gleason grade 2–6, PSA <10 ng/mL) and selected patients with low-volume intermediate-risk cancers.

Brachytherapy may be combined with EBRT (45 Gy) with or without neoadjuvant ADT for intermediate-risk cancers, but the complication rate increases.<sup>249,250</sup> Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy alone.

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. For these patients, implantation may be more difficult and there is an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, prostate size may not decline in some men and the risks of potentially increased toxicity of ADT must be weighed against the possible benefit of target reduction.

Post-implant dosimetry should be performed to document the quality of the implant.<sup>251</sup> The recommended prescribed doses for monotherapy are 145 Gy for iodine-125 and 125 Gy for palladium-103.

### **HDR Brachytherapy**

HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach that provides a “boost” dose in addition to EBRT for patients at high risk of recurrence. Combining EBRT (40–50 Gy) and HDR brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.<sup>252-255</sup> Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.<sup>256-258</sup> An analysis of a cohort of 12,745 patients with high-risk disease found that treatment with brachytherapy (HR, 0.66; 95% CI, 0.49–0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66–0.90) lowered

disease-specific mortality compared to EBRT alone.<sup>259</sup> Common boost doses include 13 to 15 Gy x 1 fraction, 8 to 11.5 Gy x 2 fractions, 5.5 to 6.5 Gy x 3 fractions, or 4.0 to 6.0 Gy x 4 fractions. Commonly used regimens for HDR treatment alone include 19 Gy x 1 fraction, 13.5 Gy x 2 fractions, 10.5 Gy x 3 fractions, and 9.5 Gy x 4 fractions.

Addition of ADT (2 or 3 years) to brachytherapy and EBRT is common for patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival reaching 87% and 91%, respectively.<sup>260,261</sup> However, it remains unclear whether the ADT component contributes to outcome improvement. D’Amico and colleagues studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease.<sup>262</sup> Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. The use of all three modalities reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14–0.73). Other analyses did not find an improvement in failure rate when ADT was added to brachytherapy and EBRT.<sup>263,264</sup>

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).<sup>265,266</sup> Vargas and colleagues<sup>267</sup> reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

### **Salvage Brachytherapy**

Brachytherapy can be considered in men with biochemical recurrence after EBRT. In a retrospective study of 24 men who had EBRT as primary therapy and permanent brachytherapy after biochemical failure, the cancer-free and biochemical relapse-free survival rates were 96% and 88%, respectively, after a median follow-up of 30 months.<sup>268</sup>

Results of a phase 2 study of salvage HDR brachytherapy after EBRT included relapse-free survival, distant metastases-free survival, and cause-specific survival rates of 68.5%, 81.5%, and 90.3%, respectively, at 5 years.<sup>269</sup> Toxicities were mostly grade 1 and 2 and included gastrointestinal toxicity and urethral strictures, and one case of Grade 3 urinary incontinence.

Data on the use of brachytherapy after permanent brachytherapy are limited, but the panel agrees that it can be considered for carefully selected patients. Decisions regarding the use of brachytherapy in the recurrent-disease setting should consider comorbidities, extent of disease, and potential complications. Brachytherapy in this setting is best performed at high-volume centers.

### Proton Therapy

Proton beam RT has been used to treat patients with cancer since the 1950s. Proponents of proton therapy argue that this form of RT could have advantages over x-ray (photon)-based radiation in certain clinical circumstances. Proton therapy and x-ray-based therapies like IMRT can deliver highly conformal doses to the prostate. Proton-based therapies will deliver less radiation dose to some of the surrounding normal tissues like muscle, bone, vessels, and fat not immediately adjacent to the prostate. These tissues do not routinely contribute to the morbidity of prostate radiation and are relatively resilient to radiation injury; therefore, the benefit of decreased dose to these types of normal, non-critical tissues has not been apparent. The critical normal structures adjacent to the prostate that can create prostate cancer treatment morbidity include the bladder, rectum, neurovascular bundles, and occasionally small bowel.

The weight of the current evidence about prostate cancer treatment morbidity supports the notion that the volume of the rectum and bladder

that receives radiobiologically high doses of radiation near the prescription radiation dose accounts for the likelihood of long-term treatment morbidity, as opposed to higher volume, lower dose exposures. Numerous dosimetric studies have been performed trying to compare x-ray-based IMRT plans to proton therapy plans to illustrate how one or the other type of treatment can be used to spare the bladder or rectum from higher dose parts of the exposure. These studies suffer from the biases and talents of the investigators who plan and create computer models of dose deposition for one therapy or the other.<sup>270</sup> Although dosimetric studies in-silico can suggest that the right treatment planning can make an IMRT plan beat a proton therapy plan and vice-versa, they do not predict accurately clinically meaningful endpoints.

Comparative effectiveness studies have been published in an attempt to compare toxicity and oncologic outcomes between proton and photon therapies. Two comparisons between men treated with proton therapy or EBRT report similar early toxicity rates.<sup>271,272</sup> A prospective quality-of-life comparison of patient-reported outcomes using the EPIC instrument between IMRT (204 patients) and proton therapy (1234 patients) concluded that “No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts” after up to 2 years of follow-up.<sup>273</sup> A Medicare analysis of 421 men treated with proton therapy and a matched cohort of 842 men treated with IMRT showed less genitourinary toxicity at 6 months for protons, although the difference disappeared after 1 year.<sup>272</sup> No other significant differences were seen between the groups. In contrast, a single-center report of prospectively collected quality-of-life data revealed significant problems with incontinence, bowel dysfunction, and impotence at 3 months, 12 months, and >2 years after treatment with proton therapy.<sup>271</sup> In that report, only 28% of men with normal erectile function maintained it after





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therapy. The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy was performed using SEER-Medicare claims data for the following long-term endpoints: gastrointestinal morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures.<sup>274</sup> With follow-up as mature as 80 months and using both propensity scoring and instrumental variable analysis, the authors concluded that men receiving IMRT therapy had statistically significantly lower gastrointestinal morbidity than patients receiving proton therapy, whereas rates of urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, hip fractures, and additional cancer therapies were statistically indistinguishable between the cohorts. However, firm conclusions regarding differences in toxicity or effectiveness of proton and photon therapy cannot be drawn because of the limitations inherent in retrospective/observational studies.

The costs associated with proton beam facility construction and proton beam treatment are high compared to the expense of building and using the more common photon linear accelerator-based practice.<sup>272</sup> The American Society for Radiation Oncology (ASTRO) has evaluated proton therapy and created a model policy to support the society's position on payment coverage for proton therapy: "At the present time, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear. While proton beam therapy is not a new technology, its use in the treatment of prostate cancer is evolving. ASTRO strongly supports allowing for coverage with evidence development for patients treated on clinical trials or within prospective registries. ASTRO believes that collecting data in these settings is essential to informing consensus on

the role of proton therapy for prostate cancer, especially insofar as it is important to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy."<sup>275,276</sup>

An ongoing prospective randomized trial is accruing patients to compare prostate proton therapy and prostate IMRT. The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics, and clinical expertise.

### Radiation for Distant Metastases

Radiation is an effective means of palliating bone metastases from prostate cancer. Isolated symptomatic bone metastases can be managed with EBRT. Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation. A short course of 8 Gy x 1 is as effective as, and less costly than, 30 Gy in 10 fractions.<sup>277</sup> In a randomized trial of 898 patients with bone metastases, grade 2–4 acute toxicity was observed less often in the 8-Gy arm (10%) than the 30-Gy arm (17%) ( $P = .002$ ); however, the retreatment rate was higher in the 8-Gy group (18%) than in the 30-Gy group (9%) ( $P < .001$ ).<sup>278</sup> In another study of 425 patients with painful bone metastases, a single dose of 8 Gy was non-inferior to 20 Gy in multiple fractions in terms of overall pain response to treatment.<sup>279</sup> Most patients should be managed with a single fraction of 8 Gy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology.<sup>280</sup>

In May 2013, the U.S. Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This

first-in-class radiopharmaceutical was approved for treatment of metastatic CRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase 3, randomized trial (ALSYMPCA) that included 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.<sup>281</sup> Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved overall survival (median 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.058–0.83;  $P < .001$ ) and prolonged time to first skeletal-related event (SRE) (median 15.6 months vs. 9.8 months). Preplanned subset analyses showed that the survival benefit of radium-223 was maintained regardless of prior docetaxel use.<sup>282</sup> Intention-to-treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.<sup>283</sup> Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.<sup>281</sup> Fecal elimination of the agent led to generally mild non-hematologic side effects, which included nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of quality of life in ALSYMPCA.<sup>284</sup>

An international, open-label, single-arm phase 3b trial of radium-223 in symptomatic and asymptomatic patients treated in an early access program showed that radium-223 can be combined safely with abiraterone or enzalutamide and suggested that it can be administered safely to asymptomatic patients.<sup>285</sup>

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with wide-spread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.<sup>280</sup> Since

many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta-emitters confer no survival advantage and are palliative. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) or samarium-153 (153Sm).<sup>286</sup>

### Other Local Therapies

Local therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent settings, with the goals of reducing side effects and matching the cancer control of other therapies. At this time, the panel recommends only cryosurgery and high intensity focused ultrasound (HIFU) as options for radiation therapy recurrence in the absence of metastatic disease.

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. In the initial disease setting, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical failure.<sup>287</sup> A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.<sup>288</sup> A study by Donnelly and colleagues<sup>289</sup> randomly assigned 244 men with T2 or T3 disease to either cryotherapy or EBRT. All patients received neoadjuvant ADT. There was no difference in 3-year overall or disease-free survival. Patients who received cryotherapy reported poorer sexual function.<sup>290</sup> For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared to EBRT in a small trial of 62 patients, although disease-specific and overall survival were similar.<sup>291</sup>



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Cryosurgery has been assessed in patients with recurrent disease after radiation therapy.<sup>292-294</sup> In one registry-based study of 91 patients, the biochemical DFS rates at 1, 3, and 5 years were 95.3%, 72.4%, and 46.5%, respectively. Adverse events included urinary retention (6.6%), incontinence (5.5%), and rectourethral fistula (3.3%).<sup>294</sup>

HIFU has been studied for initial disease<sup>295,296</sup> and radiation recurrence.<sup>297-302</sup> A prospective multiinstitutional study used HIFU in 111 patients with localized prostate cancer.<sup>295</sup> The radical treatment-free survival rate was 89% at 2 years, and continence and erectile functions were preserved in 97% and 78% of patients, respectively, at 12 months. Morbidity was acceptable, with a grade III complication rate of 13%. Analysis of a prospective registry showed that 48% of men had avoided ADT at a median follow-up of 64 months.<sup>303</sup>

HIFU has been studied for treatment of radiation recurrence.<sup>297-300</sup> Analysis of a prospective registry of men treated with HIFU for radiation recurrence revealed median biochemical recurrence-free survival 63 months, 5-year OS 88%, and cancer-specific survival 94%.<sup>304</sup> Morbidity was acceptable, with grade III/IVa complication rate 3.6%. Analysis of a separate prospective registry showed that 48% of men were able to avoid ADT at a median follow-up of 64 months.<sup>303</sup>

Other emerging local therapies, such as vascular-targeted photodynamic (VTP) therapy, warrant further study.<sup>305</sup> The multicenter, open-label, phase 3, randomized controlled CLIN1001 PCM301 trial compared VTP therapy (IV padeliporfin, optical fibres inserted into the prostate, and subsequent laser activation) to active surveillance in 413 men with low-risk prostate cancer.<sup>306</sup> After a median follow-up of 24 months, 28% of participants in the VTP arm had disease progression compared with 58% in the active surveillance arm (adjusted HR, 0.34; 95% CI, 0.24–0.46;  $P < .0001$ ). Negative prostate biopsy results were

more prevalent in the VTP group (49% vs. 14%; adjusted RR, 3.67; 95% CI, 2.53–5.33;  $P < .0001$ ). The most common serious adverse event in the VTP group was urinary retention (3 of 206 patients), which resolved within 2 months in all cases.

### Androgen Deprivation Therapy

ADT is administered as primary systemic therapy in advanced disease or as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers. Castrate levels of serum testosterone (<50 ng/dL; <1.7 nmol/L) should be achieved, because low nadir serum testosterone levels were shown to be associated with improved cause-specific survival in the PR-7 study.<sup>307</sup>

### Types of ADT

ADT can be accomplished using bilateral orchiectomy (surgical castration) or a luteinizing hormone-releasing hormone (LHRH, also known as gonadotropin-releasing hormone or GnRH) agonist or antagonist (medical castration), which appear equally effective.<sup>308</sup> In patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, anti-androgen therapy should precede or be coadministered with LHRH agonist for at least 7 days to diminish ligand binding to the androgen receptor.<sup>309,310</sup> LHRH antagonists rapidly and directly inhibit the release of androgens, unlike LHRH agonists that initially stimulate LHRH receptors prior to hypogonadism. Therefore, no initial flare is associated with these agents and no coadministration of anti-androgen is necessary.

Recent evidence suggests that orchiectomy may be safer than LHRH agonist. Four hundred twenty-nine men with metastatic prostate cancer



who underwent orchiectomy were compared to 2866 men who received LHRH agonist between 1995 and 2009. Orchiectomy was associated with lower risk of fracture, peripheral arterial disease, and cardiac-related complications although risk was similar for diabetes, deep vein thrombosis, pulmonary embolism, and cognitive disorders.<sup>311</sup> The heart and T lymphocytes have receptors for LHRH. Therefore, LHRH agonists may affect cardiac contractility, vascular plaque stability, and inflammation.<sup>312</sup>

Medical or surgical castration combined with an anti-androgen is known as combined androgen blockade. No prospective randomized studies have demonstrated a survival advantage with combined androgen blockade over the serial use of an LHRH agonist and an anti-androgen.<sup>313</sup> Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in overall survival by 5% to 20% over LHRH agonist monotherapy, but a clinical trial is necessary to test this hypothesis.<sup>314,315</sup> More complete disruption of the androgen axis (finasteride or dutasteride or anti-androgen, in addition to medical or surgical castration) provides little if any benefit over castration alone.<sup>316,317</sup> Anti-androgen monotherapy appears to be less effective than medical or surgical castration and is not recommended for primary ADT.

Diethylstilbestrol (DES) can produce safe chemical castration in many men. Gynecomastia and cardiovascular side effects occur with increasing frequency with increasing dose. Side effects are rare, and survival appears equivalent to that of other means of ADT at a 1-mg daily dose. The mechanism of action of DES remains uncertain because a 1-mg dose does not render some men castrate, and DES produces responses when used in CRPC.<sup>318</sup> Transdermal estradiol may provide similar cancer control with fewer side effects.<sup>319</sup> The ongoing PATCH clinical trial demonstrated similar rates of castrate levels of

testosterone, PSA response, and side effects in 85 men treated with LHRH agonist and 168 men treated with 100 mcg/24 hours estrogen patches twice weekly.<sup>320</sup> Quality-of-life outcomes and the experience of vasomotor symptoms were better at 6 months in the transdermal group compared with the agonist group, but rates of significant gynecomastia were higher in the transdermal group (37% vs. 5%).<sup>321</sup> The PATCH trial continues enrollment in order to assess survival (NCT00303784).

### ADT for Patients with Low-Risk Disease

In the community, ADT has been used commonly as primary therapy for early-stage, low-risk disease, especially in the elderly. This practice has been challenged by a large cohort study of 66,717 elderly men with T1-T2 tumors.<sup>322</sup> No 15-year survival benefit was found in patients receiving ADT compared to observation alone. Similarly, another cohort study of 15,170 men diagnosed with clinically localized prostate cancer who were not treated with curative intent therapy reported no survival benefit from primary ADT after adjusting for demographic and clinical variables.<sup>323</sup> Placing patients with early prostate cancer on ADT should not be routine practice.

### ADT for Patients with Intermediate-Risk Disease

The addition of short-term ADT to radiation improved overall and cancer-specific survival in three randomized trials containing 20% to 60% of men with intermediate-risk prostate cancer (Trans Tasman Radiation Oncology Group [TROG] 9601, Dana Farber Cancer Institute [DFCI] 95096, and Radiation Therapy Oncology Group [RTOG] 9408).<sup>324-327</sup> Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).<sup>328</sup> Results of the EORTC 22991 trial showed that the addition of 6 months of ADT significantly improved biochemical DFS compared with radiation alone in intermediate-risk (75% of study population) and high-risk men.<sup>329</sup>



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RTOG 9910 and RTOG 9902 reinforced two important principles concerning the optimal duration of ADT and use of systemic chemotherapy in conjunction with EBRT.<sup>330,331</sup> RTOG 9910 is a phase 3 randomized trial targeting men with intermediate-risk prostate cancer that compared 4 months to 9 months of ADT. RTOG 9408 had previously shown that 4 months of ADT combined with EBRT improved survival in men with intermediate-risk disease compared to EBRT alone.<sup>326</sup> Consistent with earlier studies, RTOG 9910 demonstrated that there is no reason to extend ADT beyond 4 months when given in conjunction with EBRT in men with intermediate-risk disease. RTOG 9902 compared long-term ADT and EBRT with and without paclitaxel, estramustine, and etoposide (TEE) chemotherapy in men with locally advanced, high-risk prostate cancer. This trial demonstrated the importance of performing large phase 3 trials. In a randomized cohort of 397 patients with a median follow-up of 9.2 years, results demonstrated no significant difference in ADT+EBRT versus ADT+EBRT+TEE in overall survival (65% vs. 63%;  $P = .81$ ), biochemical failure (58% vs. 54%;  $P = .82$ ), distant metastases (16% vs. 14%;  $P = .42$ ), or disease-free survival (22% vs. 26%;  $P = .61$ ), but a substantial increase in toxicity (3.9% vs. 0% treatment-related deaths), which resulted in early closure of the trial.<sup>332</sup> Thus, the fact that 6 months of ADT improved survival compared to EBRT alone does not mean it is better than 4 months of ADT, and the fact that systemic chemotherapy is effective in one setting (high-volume metastatic disease or CRPC) should not lead to the assumption that it will be beneficial in other settings (eg, high-risk localized disease).<sup>333,334</sup>

### ADT for Patients with High-Risk or Very-High-Risk Disease

ADT combined with EBRT is an effective primary treatment for patients at high risk or very high risk, as discussed in the *Radiation Therapy* section. Combination therapy was associated consistently with

improved disease-specific and overall survival compared to single-modality treatment in randomized phase 3 studies.<sup>226,227,229,230</sup>

Increasing evidence favors long-term over short-term neoadjuvant/concurrent/adjuvant ADT for patients with high- and very-high-risk disease. The RTOG 9202 trial included 1521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during EBRT.<sup>335</sup> They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group was superior for all endpoints except overall survival. A subgroup analysis of patients with a Gleason score of 8 to 10 found an advantage in overall survival for long-term ADT (32% vs. 45%,  $P = .0061$ ). The European Organization for Research and Treatment of Cancer (EORTC) 22961 trial also showed superior survival when 2.5 years of ADT were added to EBRT given with 6 months of ADT in 970 patients, most of whom had T2c-T3, N0 disease.<sup>336</sup> The DART01/05 GICOR trial also reported similar results in men with high-risk disease.<sup>337</sup> In a secondary analysis of RTOG 8531 that mandated lifelong ADT, those who adhered to the protocol had better survival than those who discontinued ADT within 5 years.<sup>338</sup>

### Adjuvant ADT after Radical Prostatectomy

The role of adjuvant ADT after radical prostatectomy is restricted to cases where positive pelvic lymph nodes are found, although reports in this area reveal mixed findings. Messing and colleagues randomly assigned patients who were found to have positive lymph nodes at the time of radical prostatectomy to immediate ADT or observation.<sup>339</sup> At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in overall survival (HR, 1.84; 95% CI, 1.01–3.35). However, a meta-analysis resulted in a recommendation against ADT for pathologic lymph node metastatic prostate cancer in the ASCO





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guidelines.<sup>313</sup> A cohort analysis of 731 men with positive nodes failed to demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.<sup>340</sup>

Anti-androgen monotherapy (bicalutamide) after completion of primary treatment was investigated as an adjuvant therapy in patients with localized or locally advanced prostate cancer, but results did not support its use in this setting.<sup>341,342</sup>

### ADT for Biochemical Recurrence

Patients with an increasing PSA level and with no symptomatic or clinical evidence of cancer after definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. Timing of ADT for patients whose only evidence of cancer is increasing PSA is influenced by PSA velocity, patient and physician anxiety, the short-term and long-term side effects of ADT, and underlying comorbidities of the patient. Early ADT is acceptable, but an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (ie, what level of PSA) remain controversial. The multicenter phase 3 TROG 03.06/VCOG PR 01-03 [TOAD] trial randomized 293 men with PSA relapse after operation or radiation (n = 261) or who were not considered for curative treatment (n = 32) to immediate ADT or ADT delayed by a recommended interval of ≥2 years.<sup>343</sup> Five-year OS was improved in the immediate therapy arm compared with the delayed therapy arm (91.2% vs. 86.4%; log-rank  $P = .047$ ). The panel believes that the benefit of early ADT is uncertain and must be balanced against the risk of ADT side effects. Patients with an elevated PSA and/or a shorter PSA doubling time (rapid PSA velocity)

and an otherwise long life expectancy should be encouraged to consider ADT earlier.

### *Intermittent Versus Continuous ADT (Non-Metastatic)*

ADT is associated with substantial side effects, which generally increase with the duration of treatment. Intermittent ADT is an approach based on the premise that cycles of androgen deprivation followed by re-exposure may delay “androgen independence,” reduce treatment morbidity, and improve quality of life.<sup>344,345</sup>

The Canadian-led PR.7 trial was a phase 3 trial of intermittent versus continuous ADT in patients with non-metastatic prostate cancer who experienced biochemical failure after radical prostatectomy.<sup>346</sup> One thousand three hundred eighty-six patients with PSA >3 ng/mL after RT were randomly assigned to intermittent ADT or continuous ADT. At a median follow-up of 6.9 years, the intermittent approach was non-inferior to continuous ADT with respect to overall survival (8.8 vs. 9.1 years, respectively; HR, 1.02; 95% CI, 0.86–1.21). More patients died from prostate cancer in the intermittent ADT arm (120 of 690 patients) than the continuous ADT arm (94 of 696 patients), but this was balanced by more non-prostate cancer deaths in the continuous ADT arm. Physical function, fatigue, urinary problems, hot flashes, libido, and erectile dysfunction showed modest improvement in the intermittent ADT group. The test population was heterogenous, so it remains unclear which of these asymptomatic patients benefitted from treatment. It is possible that many of these patients could have delayed ADT without harm. The test population had a low disease burden and 59% of deaths in the trial were not related to prostate cancer. Follow-up longer than 6.9 years may be required for disease-specific deaths to out-balance deaths by other causes.



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An unplanned Cox regression analysis of the trial showed that men with Gleason sum >7 in the continuous ADT arm had a median survival (8 years) that was 14 months longer than those with the same Gleason sum in the intermittent ADT arm (6.8 years).<sup>346</sup> In this situation, patients should be given the option to weigh the effects of ADT on quality of life against a possible impact on survival, although pathology was not centrally reviewed and the study was not powered to detect small differences in survival based on Gleason sum.<sup>347</sup>

The multinational European ICELAND trial randomized 702 participants with locally advanced or biochemically recurrent prostate cancer to continuous or intermittent ADT.<sup>348</sup> Clinical outcomes, which included time to PSA progression, PSA progression-free survival, overall survival, mean PSA levels over time, quality of life, and adverse events, were similar between the arms. A 2015 meta-analysis identified 6 randomized controlled trials comparing continuous with intermittent ADT in men with locally advanced prostate cancer and found no difference in mortality and progression and an advantage of the intermittent approach in terms of quality of life and adverse effects.<sup>349</sup>

### ADT for Nodal or Metastatic Disease

Controversy remains about the timing and duration of ADT when local therapy has failed. Most believe that early ADT is best, but early ADT is associated with increased side effects and development of the metabolic syndrome. A review of the older literature from both clinical practice and preclinical models provides little evidence that the timing of ADT matters. The average time from lymph node metastasis to bone metastasis is 3 years and survival is approximately 3 more years with ADT and perhaps 5 more years with ADT and new agents. In Dr. Messing's ECOG trial, 98 men found to have lymph node metastases at radical prostatectomy were randomized to immediate continuous ADT

or observation. In the immediate ADT arm of 47 patients, 30 remained alive, 29 of whom were prostate-cancer-recurrence-free and 26 of whom were PSA-failure-free after a median follow-up of 11.9 years (range, 9.7–14.5 years for survivors).<sup>339,350</sup> However, these results differ from a SEER Medicare, population-based test of ADT published subsequently.<sup>340</sup> The SEER Medicare-based study of men who underwent radical prostatectomy and had positive lymph nodes used propensity matching to compare men who received ADT within 120 days to those who were observed. The groups had similar median and range of follow-up for survivors, but overall survival and prostate cancer-specific survival were similar. The Messing study occurred prior to the PSA era, but the studies are similar in almost all other respects. The Messing study done in 98 men showed almost unbelievable benefit, and the population-based study of 731 men showed no benefit.

The EORTC 30846 trial randomized 234 treatment-naïve patients with node-positive prostate cancer to immediate versus delayed ADT.<sup>351</sup> At 13 years, the authors report similar survival between the two arms, although the study was not powered to show non-inferiority. Hence, the preponderance of the evidence supports a more measured approach to the use of ADT for lymph node-metastatic prostate cancer.

ADT is the gold standard of initial treatment for patients with metastatic disease at presentation.<sup>313</sup> A PSA value of 4 ng/mL or less after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.<sup>352</sup>

### *Intermittent versus Continuous ADT (Metastatic)*

Hussain and colleagues<sup>353</sup> conducted the SWOG (Southwest Oncology Group) 9346 trial to compare intermittent and continuous ADT in patients with metastatic disease. After 7 months of induction ADT, 1535 patients whose PSA dropped to 4 ng/mL or below (thereby



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demonstrating androgen sensitivity) were randomized to intermittent or continuous ADT. At a median follow-up of 9.8 years, median survival was 5.1 years for the intermittent ADT arm and 5.8 years for the continuous ADT arm. The HR for death with intermittent ADT was 1.10 with a 90% CI between 0.99 and 1.23, which exceeded the pre-specified upper boundary of 1.20 for non-inferiority. The authors stated that the survival results were inconclusive, and that a 20% greater mortality risk with the intermittent approach cannot be ruled out. The study demonstrated better erectile function and mental health in patients receiving intermittent ADT at 3 months, but the difference became insignificant thereafter, most likely due to contamination of assessments of those on the intermittent arm who may have returned to ADT at the pre-specified time points.

In a post-hoc stratification analysis of the trial, patients with minimal disease had a median survival of 5.4 years when receiving intermittent ADT versus 6.9 years when receiving continuous ADT (HR, 1.19; 95% CI, 0.98–1.43).<sup>353</sup> The median survival was 4.9 years in the intermittent ADT arm compared to 4.4 years in the continuous ADT arm for patients with extensive disease (HR, 1.02; 95% CI, 0.85–1.22). These subgroup analyses are hypothesis-generating.

Several meta-analyses of randomized controlled trials reported no difference in survival between intermittent ADT and continuous ADT.<sup>354-356</sup> Another recent analysis concluded that the non-inferiority of intermittent to continuous ADT in terms of survival has not been demonstrated clearly.<sup>357</sup> Still, the intermittent approach leads to marked improvement in quality of life compared to the continuous approach in most studies, and the panel believes that intermittent ADT should be strongly considered.

A more personalized approach could treat all patients with metastatic disease with ADT. After 7 months of ADT, patients can be assigned a risk category based on the PSA value at that time point<sup>352</sup>: low risk is defined by a PSA less than 0.2 ng/mL (median survival of 75 months); intermediate risk is defined by a PSA between 0.2 and 4.0 ng/mL (median survival of 44 months), and high risk is defined by a PSA higher than 4.0 ng/mL (median survival of 13 months). Those patients who have few or no symptoms related to ADT after 7 months of therapy will not benefit from intermittent ADT in terms of quality of life, and therefore continuous therapy makes sense because it is easier to administer.<sup>347</sup> However, for those patients with significant side effects impacting quality of life, intermittent ADT should be considered for those with low or intermediate risk after a discussion about the impact on survival. A final consideration is based on a subgroup analysis of S9346 that suggested that those who present initially with pain have better survival on continuous therapy than intermittent therapy.

### Adverse Effects of Traditional ADT

ADT has a variety of adverse effects including hot flashes, vasomotor instability, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes, acute kidney injury, and cardiovascular disease.<sup>358-360</sup> Recent evidence suggests that a link between ADT and cognitive decline or future Alzheimer's disease may exist, although data are inconsistent, the risk is low, and the link remains to be proven.<sup>361-363</sup> In general, the side effects of continuous ADT increase with the duration of treatment. Patients and their medical providers should be advised about these risks prior to treatment.

### Bone Health During ADT

ADT is associated with greater risk for clinical fractures. In large population-based studies, for example, ADT was associated with a 21%



to 54% relative increase in fracture risk.<sup>364-366</sup> Longer treatment duration conferred greater fracture risk. Age and comorbidity also were associated with higher fracture incidence. In a population-based cohort of 3295 patients, surgical castration was associated with a significantly lower risk of fractures than medical castration using a GnRH agonist (HR, 0.77; 95% CI, 0.62–0.94;  $P = .01$ ).<sup>312</sup> ADT increases bone turnover and decreases bone mineral density,<sup>367-370</sup> a surrogate for fracture risk in patients with non-metastatic disease. Bone mineral density of the hip and spine decreases by approximately 2% to 3% per year during initial therapy. Most studies have reported that bone mineral density continues to decline steadily during long-term therapy. ADT significantly decreases muscle mass,<sup>371</sup> and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.<sup>372</sup> The National Osteoporosis Foundation guidelines include: 1) supplemental calcium (1200 mg daily) and vitamin D3 (800–1000 IU daily) for all men older than age 50 years; and 2) additional treatment for men when the 10-year probability of hip fracture is  $\geq 3\%$  or the 10-year probability of a major osteoporosis-related fracture is  $\geq 20\%$ . Fracture risk can be assessed using the algorithm FRAX®, recently released by WHO.<sup>373</sup> ADT should be considered “secondary osteoporosis” using the FRAX® algorithm.

Earlier randomized controlled trials demonstrated that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT.<sup>374-376</sup> In 2011, the FDA approved denosumab as a treatment to prevent bone loss and fractures during ADT. Denosumab binds to and inhibits the receptor activator of NF- $\kappa$ B ligand (RANKL) to blunt osteoclast function and delay generalized bone resorption and local bone destruction. Approval was based on a phase 3 study that

randomized 1468 patients with non-metastatic prostate cancer undergoing ADT to either biannual denosumab or placebo. At 24 months, denosumab increased bone mineral density by 6.7% and reduced fractures (1.5% vs. 3.9%) compared to placebo.<sup>377</sup> Denosumab also was approved for prevention of SREs in patients with bone metastasis (see *Chemotherapy and Immunotherapy*).

Currently, treatment with denosumab (60 mg every 6 months), zoledronic acid (5 mg IV annually), or alendronate (70 mg PO weekly) is recommended when the absolute fracture risk warrants drug therapy. A baseline dual-energy x-ray absorptiometry (DEXA) scan before start of therapy and a follow-up DEXA scan after one year of therapy is recommended by the International Society for Clinical Densitometry to monitor response. Use of biochemical markers of bone turnover is not recommended. There are no existing guidelines on the optimal frequency of vitamin D testing, but vitamin D levels can be measured when DEXA scans are obtained.

### **Diabetes and Cardiovascular Disease**

In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease.<sup>378</sup> After controlling for other variables, which included age and comorbidity, ADT with a GnRH agonist was associated with increased risk for new diabetes (HR, 1.44;  $P < .001$ ), coronary artery disease (HR, 1.16;  $P < .001$ ), and myocardial infarction (HR, 1.11;  $P = .03$ ). Studies that evaluated the potential relationship between ADT and cardiovascular mortality have produced mixed results.<sup>328,378-384</sup> In a Danish cohort of 31,571 patients with prostate cancer, medical castration was associated with an increased risk for myocardial infarction (HR, 1.31; 95% CI, 1.16–1.49) and stroke (HR, 1.19; 95% CI, 1.06–1.35) whereas surgical castration was not.<sup>385</sup> Other population-based studies resulted in similar findings.<sup>312,386</sup> Men with recent history of cardiovascular disease appear to have higher



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risk,<sup>387</sup> and increased physical activity may decrease the symptoms and cardiovascular side effects of men treated with ADT.<sup>388</sup>

Several mechanisms may contribute to greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.<sup>371,389,390</sup> ADT with a GnRH agonist increases fasting plasma insulin levels<sup>391,392</sup> and decreases insulin sensitivity.<sup>393</sup> ADT also increases serum levels of cholesterol and triglycerides.<sup>391,394</sup>

Cardiovascular disease and diabetes are leading causes of morbidity and mortality in the general population. Based on the observed adverse metabolic effects of ADT and the association between ADT and higher incidence of diabetes and cardiovascular disease, screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended for men receiving ADT. Whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from those of the general population remains uncertain.

### Hormone Therapy for CRPC

Most men with advanced disease eventually stop responding to traditional ADT and are categorized as castration-recurrent (also known as castration-resistant). Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of men receiving ADT.<sup>395,396</sup> Androgen signaling from non-gonadal sources in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the metastatic CRPC setting dramatically changed the paradigm of CRPC treatment.

### **Abiraterone Acetate**

In April 2011, the FDA approved the androgen synthesis inhibitor, abiraterone acetate (abiraterone), in combination with low-dose prednisone, for the treatment of men with metastatic CRPC who have received prior chemotherapy containing docetaxel.

FDA approval in the post-docetaxel setting was based on the results of a phase 3, randomized, placebo-controlled trial (COU-AA-301) in men with metastatic CRPC previously treated with docetaxel-containing regimens.<sup>397,398</sup> Patients were randomized to receive either abiraterone 1000 mg orally once daily (n = 797) or placebo once daily (n = 398), and both arms received daily prednisone. In the final analysis, median survival was 15.8 vs. 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86;  $P < .0001$ ).<sup>398</sup> Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.<sup>398,399</sup>

FDA approval in the pre-docetaxel setting occurred on December 10, 2012 and was based on the randomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n = 546) versus prednisone alone (n = 542) in men with asymptomatic or minimally symptomatic, metastatic CRPC.<sup>400</sup> Most men in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary endpoint of radiographic progression-free survival was improved by treatment from 8.3 to 16.5 months (HR, 0.53;  $P < .001$ ). Overall survival was improved at final analysis with a median follow-up of 49.2 months (34.7 months vs. 30.3 months; HR, 0.81; 95% CI, 0.70–0.93;  $P = .003$ ).<sup>401</sup> Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA progression-free survival improved significantly with abiraterone treatment, and PSA declines (62% vs. 24% with >50%





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decline) and radiographic responses (36% vs. 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%). Thus, monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis, at least initially is warranted during abiraterone/prednisone therapy. Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

### Enzalutamide

On August 31, 2012, the FDA approved enzalutamide, an anti-androgen, for treatment of men with metastatic CRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase 3, placebo-controlled trial (AFFIRM).<sup>402,403</sup> AFFIRM randomized 1199 men to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was overall survival. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63;  $P < .001$ ). Survival was improved in all subgroups analyzed. Secondary endpoints also were improved significantly, which included the proportion of men with >50% PSA decline (54% vs. 2%), radiographic response (29% vs. 4%), radiographic progression-free survival (8.3 vs. 2.9 months), and time to first SRE (16.7 vs. 13.3 months). Quality of life measured using

validated surveys was improved with enzalutamide compared to placebo. Adverse events were mild, and included fatigue (34% vs. 29%), diarrhea (21% vs. 18%), hot flushes (20% vs. 10%), headache (12% vs. 6%), and seizures (0.6% vs. 0%). The incidence of cardiac disorders did not differ between the arms. Enzalutamide is dosed at 160 mg daily. Patients in the AFFIRM study were maintained on GnRH agonist/antagonist therapy and could receive bone supportive care medications. The seizure risk in the enzalutamide FDA label was 0.9% versus 0.6% in the manuscript.<sup>402,404</sup>

Another phase 3 trial studied enzalutamide in the pre-chemotherapy setting. The PREVAIL study randomly assigned 1717 patients with chemotherapy-naïve metastatic prostate cancer to daily enzalutamide or placebo.<sup>405,406</sup> The study was stopped early due to benefits shown in the treatment arm. Compared to the placebo group, the enzalutamide group showed improved median progression-free survival (20.0 months vs. 5.4 months) and median overall survival (35.3 months vs. 31.3 months). Improvements in all secondary endpoints also were observed (eg, the time until chemotherapy initiation or first SRE).

Two randomized clinical trials have reported that enzalutamide may be superior to bicalutamide for cancer control in metastatic CRPC. The TERRAIN study randomized 375 men with treatment-naïve, metastatic CRPC to 160 mg/d enzalutamide or 50 mg/d bicalutamide in a 1:1 manner.<sup>407</sup> The enzalutamide group had significantly better progression-free survival (defined as PSA progression, soft tissue progression, or development of additional bony metastases) compared to the bicalutamide group (median time to progression, 15.7 vs. 5.8 months; HR, 0.44; 95% CI, 0.34–0.57).

The STRIVE trial randomized 396 men with M0 or M1 treatment-naïve CRPC to 160 mg/d enzalutamide or 50 mg/d bicalutamide in a 1:1

manner.<sup>408</sup> The primary endpoint in this study was progression-free survival, defined as either PSA progression, radiographic progression of disease, or death from any cause. Enzalutamide reduced the risk of progression or death by 76% compared to bicalutamide (HR, 0.24; 95% CI, 0.18–0.32). These studies demonstrated that enzalutamide extended progression-free survival better than bicalutamide in men choosing an anti-androgen for secondary hormonal therapy treatment of CRPC. Bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.

Thus, enzalutamide represents a treatment option for men in both the pre-docetaxel and post-docetaxel metastatic CRPC setting and is a reasonable choice for men who are not candidates for chemotherapy.

### Chemotherapy and Immunotherapy

Recent research has expanded the therapeutic options for patients with metastatic CRPC depending on the presence or absence of symptoms.

#### Docetaxel

Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916).<sup>334,409,410</sup> TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 men.<sup>409</sup> Every-3-week docetaxel resulted in higher median overall survival than mitoxantrone (18.9 vs. 16.5 months;  $P = .009$ ). This survival benefit was maintained at extended follow-up.<sup>410</sup> The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.<sup>334</sup> Docetaxel is FDA-approved for metastatic CRPC. The standard regimen is every 3 weeks. An alternative to every-3-week docetaxel is a biweekly regimen

of 50 mg/m<sup>2</sup>. This regimen is based on a large randomized phase 2 trial of 346 men with metastatic CRPC randomized to either every-2-week docetaxel or every-3-week docetaxel, each with maintenance of ADT and prednisone.<sup>411</sup> Men treated with the every-2-week regimen survived an average of 19.5 months compared to 17.0 months with the every-3-week regimen ( $P = .015$ ). Time-to-progression and PSA decline rate favored every-2-week therapy. Tolerability was improved with every-2-week docetaxel; febrile neutropenia rate was 4% versus 14% and other toxicities and overall quality of life were similar.

Docetaxel is included as an upfront option for men with progressive androgen-stimulated prostate cancer and distant metastases based on results from 2 phase 3 trials (ECOG 3805/CHAARTED and STAMPEDE).<sup>412,413</sup> CHAARTED randomized 790 men with metastatic, androgen-stimulated prostate cancer to docetaxel plus ADT or ADT alone.<sup>413</sup> The patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 months vs. 44.0 months; HR, 0.61; 95% CI, 0.47–0.80;  $P < .001$ ). Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.60; 95% CI, 0.45–0.81;  $P < .001$ ). Men with low-volume disease in CHAARTED may have derived a survival benefit from the inclusion of docetaxel (HR, 0.60; 95% CI, 0.32–1.13;  $P = .11$ ), although median overall survival was not reached for either arm, and the number of patients was low.

The STAMPEDE trial, a multi-arm, multistage phase 3 trial, included patients with both M0 and M1 androgen-stimulated prostate cancer.<sup>412</sup> The results in the M1 population essentially confirmed the survival advantage of adding docetaxel to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1087 men with metastatic disease, but the median overall survival for all patients with M1 disease was 5.4 years in the ADT-plus-docetaxel arm versus 3.6



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years in the ADT-only arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHAARTED). The results of the STAMPEDE trial seem to confirm the results of the CHAARTED trial.

The panel added the use of docetaxel in combination with ADT and EBRT in fit men with high- and very-high-risk localized disease in the 2016 version of these guidelines. This recommendation is supported by results of the GETUG 12 trial, which randomized 413 men with high- or very-high risk prostate cancer to IMRT and ADT or ADT, docetaxel, and estramustine.<sup>414</sup> After median follow-up 8.8 years, 8-year relapse-free survival was 62% in the combination therapy arm and 50% in the ADT-only arm (adjusted HR, 0.71; 95% CI, 0.54–0.94;  $P = .017$ ). Estramustine has been shown to increase side effects without enhancing efficiency when added to docetaxel and is not recommended.<sup>415</sup>

### Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semi-synthetic taxane derivative, for men with metastatic CRPC previously treated with a docetaxel-containing regimen. An international randomized phase 3 trial (TROPIC) randomized 755 men with progressive metastatic CRPC to receive cabazitaxel 25 mg/m<sup>2</sup> or mitoxantrone 12 mg/m<sup>2</sup>, each with daily prednisone.<sup>416</sup> A 2.4 month improvement in overall survival was demonstrated with cabazitaxel compared to mitoxantrone (HR, 0.72;  $P < .0001$ ). The improvement in survival was balanced against a higher toxic death rate with cabazitaxel (4.9% vs. 1.9%), which was due, in large part, to differences in rates of sepsis and renal failure. Febrile neutropenia was observed in 7.5% of cabazitaxel-treated men vs. 1.3% of mitoxantrone-treated men. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated men,

which indicated the need for vigilance and treatment or prophylaxis in this setting to prevent febrile neutropenia. The survival benefit was sustained at an updated analysis with a median follow-up of 25.5 months.<sup>417</sup>

The phase 3 open-label, multinational, non-inferiority PROSELICA study compared 20 mg/m<sup>2</sup> cabazitaxel with 25 mg/m<sup>2</sup> cabazitaxel in 1200 patients with mCRPC who progressed on docetaxel.<sup>418</sup> The lower dose was found to be noninferior to the higher dose for median overall survival (13.4 mo [95% CI, 12.19–14.88] vs. 14.5 mo [95% CI, 13.47–15.28]), and grade 3/4 adverse events were decreased (39.7% vs. 54.5%). In particular, grade 4 neutropenia rates were 21.3% and 48.6% for the lower and higher dose groups, respectively. Cabazitaxel at 25 mg/m<sup>2</sup> every 3 weeks, with or without growth factor support remains standard of care for fit patients. However, in frail patients, cabazitaxel at 20 mg/m<sup>2</sup> every 3 weeks, with or without growth factor support, can be considered.

Recent results from the phase 3 FIRSTANA study suggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.<sup>419</sup> Median overall survival, the primary endpoint, was similar between 20 mg/m<sup>2</sup> cabazitaxel, 25 mg/m<sup>2</sup> cabazitaxel, and 75 mg/m<sup>2</sup> docetaxel (24.5 mo, 25.2 mo, and 24.3 mo, respectively). Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m<sup>2</sup> (12% vs. 25%). Therefore, patients who are not candidates for docetaxel, who are intolerant of docetaxel, or who have pre-existing mild peripheral neuropathy should be considered for cabazitaxel.

### Sipuleucel-T

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. This autologous





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cancer “vaccine” involves collection of the white blood cell fraction containing antigen-presenting cells from each patient, exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein), and subsequent reinfusion of the cells. The pivotal study was a phase 3, multicenter, randomized, double-blind trial (D9902B).<sup>420</sup> Five hundred twelve patients with minimally symptomatic or asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or placebo. Median survival in the vaccine arm was 25.8 months compared to 21.7 months in the control arm. Sipuleucel-T treatment resulted in 22% reduction in mortality risk (HR, 0.78; 95% CI, 0.61–0.98;  $P = .03$ ). Common complications included mild to moderate chills (54.1%), pyrexia (29.3%), and headache (16.0%), which usually were transient.

### Agents Related to Bone Health in CRPC

In a multicenter study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every 3 weeks or placebo.<sup>421</sup> At 15 months, fewer men in the zoledronic acid 4-mg group than men in the placebo group had SREs (33% vs. 44%;  $P = .02$ ). An update at 24 months also revealed an increase in the median time to first SRE (488 days vs. 321 days;  $P = .01$ ).<sup>422</sup> No significant differences were found in overall survival. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications.

Denosumab was compared to zoledronic acid in a randomized, double-blind, placebo-controlled study in men with CRPC.<sup>423</sup> The absolute incidence of SREs was similar in the 2 groups; however, the median time to first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid (20.7 vs. 17.1 months;  $P = .0002$  for non-inferiority,  $P = .008$  for superiority). The rates of important SREs with denosumab

were similar to zoledronic acid and included spinal cord compression (3% vs. 4%), need for radiation (19% vs. 21%), and pathologic fracture (14% vs. 15%).

Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs. 6%), arthralgias, and osteonecrosis of the jaw (ONJ, 1%–2% incidence). Most, but not all, patients who develop ONJ have preexisting dental problems.<sup>424</sup>

## NCCN Recommendations

### Initial Prostate Cancer Diagnosis

Initial suspicion of prostate cancer is based on an abnormal DRE or an elevated PSA level. A separate NCCN Guidelines Panel has written guidelines for prostate cancer early detection (see [NCCN Guidelines for Prostate Cancer Early Detection](#)). Definitive diagnosis requires biopsies of the prostate, usually performed by a urologist using a needle under TRUS guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2010 classification from the AJCC Staging Manual, 7<sup>th</sup> edition.<sup>425</sup> However, NCCN treatment recommendations are based on risk stratification rather than AJCC prognostic grouping.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Guidelines Panel favors pathology synoptic reports from the College of American Pathologists (CAP) that comply with the Commission on Cancer requirements.<sup>426</sup>





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### Initial Clinical Assessment and Staging Evaluation

For patients with a life expectancy of 5 years or less and without clinical symptoms, further workup or treatment should be delayed until symptoms develop. ADT or EBRT may be considered for selected patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastases, are likely within 5 years. Patients with advanced cancer may be candidates for observation if the risks and complications of therapy are judged to be greater than the benefit in terms of prolonged life or improved quality of life.

For symptomatic patients and/or those with a life expectancy of greater than 5 years, a bone scan is appropriate for patients with any of the following: 1) T1 disease with PSA over 20 ng/mL or T2 disease with PSA over 10 ng/mL<sup>427</sup>; 2) Gleason score 8 or higher/Gleason grade group 4-5; 3) T3 to T4 disease; or 4) symptomatic disease. Pelvic CT or MRI scanning is recommended for T3 or T4 disease, or T1 or T2 disease when a nomogram indicates a greater than 10% chance of lymph node involvement, although staging studies may not be cost effective until the chance of lymph node positivity reaches 45%.<sup>428</sup>

Alternative approaches to imaging based on the likelihood of a positive study rather than by risk group alone have been proposed based on data from a quality improvement collaborative in the state of Michigan.<sup>75</sup> For pelvic CT, the following criteria would identify almost all men with a positive study and reduce the number of negative studies: 1) PSA level >20 ng/mL, or 2) Gleason score ≥8/Gleason grade group 4-5, or 3) clinical stage ≥T3. For bone scan, the recommended criteria include: 1) PSA level >20 ng/mL, or 2) Gleason score ≥8/Gleason grade group 4-5.<sup>76</sup> Use of these criteria may reduce the number of negative study results without missing a significant number of positive studies. Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging.

NCCN panelists voiced concern about inappropriate use of PET imaging. FDG or fluoride PET is not recommended for initial assessment.

The staging workup is used to categorize patients according to their risk of recurrence or disease progression/recurrence into those with clinically localized disease at very low, low, intermediate, or high risk, or those with locally advanced at very high risk, or those with metastatic disease.

### Very Low Risk

Men with all of the following tumor characteristics are categorized in the very-low-risk group: clinical stage T1c, biopsy Gleason score ≤6/Gleason grade group 1, PSA <10 ng/mL, presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <0.15 ng/mL/g. Given the potential side effects of definitive therapy, men in this group who have an estimated life expectancy of less than 10 years should undergo observation (monitoring no more often than every 6 months). Unlike active surveillance, observation schedules do not involve biopsies. Men with very low risk and a life expectancy of 10 to 20 years should undergo active surveillance. For patients who meet the very-low-risk criteria but who have a life expectancy of 20 years or above, the NCCN Panel agreed that active surveillance, EBRT or brachytherapy, or radical prostatectomy are all viable options and should be discussed thoroughly.

### Low Risk

The NCCN Guidelines define the low-risk group as patients with clinical stage T1 to T2a, Gleason score 6/Gleason grade group 1, and serum PSA level <10 ng/mL. Observation is recommended for men with low-risk prostate cancer and a life expectancy of less than 10 years. If



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the patient's life expectancy is 10 years or more, initial treatment options include: 1) active surveillance; 2) EBRT or brachytherapy; or 3) radical prostatectomy with or without a PLND if the predicted probability of pelvic lymph node involvement is  $\geq 2\%$ . ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN Guidelines Panel.

Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy.

### Intermediate Risk

The NCCN Guidelines define the intermediate-risk group as patients with clinical stage T2b to T2c, Gleason score 7/Gleason grade group 2-3, or PSA value of 10 ng/mL to 20 ng/mL. Patients with multiple adverse factors may be shifted to the high-risk group.

Options for patients with life expectancy less than 10 years include: 1) observation; 2) EBRT with or without ADT (4–6 months), and with or without brachytherapy; and 3) brachytherapy alone for selected patients with low-volume disease.

Initial treatment options for patients with an expected survival of  $\geq 10$  years include: 1) radical prostatectomy and PLND if the predicted probability of lymph node metastasis is  $\geq 2\%$ ; 2) EBRT with or without 4 to 6 months of ADT, and with or without brachytherapy; and 3) brachytherapy alone for selected patients with low-volume disease. In addition, the panel defines a favorable subset of men with intermediate-risk prostate cancer for whom active surveillance may be considered (ie, predominant Gleason grade 3 [ie, Gleason score 3 + 4 = 7/Gleason grade group 2], percentage of positive biopsy cores  $< 50$ , and  $\leq 1$  NCCN intermediate risk factor).<sup>23</sup> Active surveillance is not recommended for

patients with a life expectancy  $> 10$  years (category 1) if they fall in the unfavorable subset of intermediate risk.

The literature on outcomes of active surveillance in men with intermediate-risk prostate cancer is limited. In the PIVOT trial, men with clinically localized prostate cancer and life expectancy  $\geq 10$  years were randomized to radical prostatectomy or observation.<sup>429</sup> Of the 120 participants with intermediate-risk disease who were randomized to observation, only 13 died from prostate cancer, a non-significant difference compared with 6 prostate-cancer deaths in 129 participants with intermediate-risk disease in the radical prostatectomy arm (HR, 0.50; 95% CI, 0.21–1.21;  $P = .12$ ). The median 10-year follow-up and less-than-average health of men in the PIVOT study suggest that men with competing risks may safely be offered active surveillance. Other prospective studies of active surveillance that included men with intermediate-risk prostate cancer resulted in prostate cancer-specific survival rates of 94% to 100% for the full cohorts.<sup>99,100,102</sup> The panel interpreted these data to show that a subset of men with intermediate-risk prostate cancer may be considered for active surveillance, although longer-term follow-up is needed in these and others studies to increase confidence about the risks and benefits of active surveillance in this population.

The panel believes that active surveillance may be considered for men with favorable intermediate-risk prostate cancer, but should be approached with caution, include informed decision-making, and use close monitoring for progression.

### High Risk

Men with prostate cancer that is clinical stage T3a, Gleason score 8 to 10/Gleason grade group 4-5, or PSA level greater than 20 ng/mL are categorized by the panel as high risk. Patients with multiple adverse



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factors may be shifted to the very high-risk category. The preferred treatment is EBRT in conjunction with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT (category 1); ADT alone is insufficient. In particular, patients with low-volume, high-grade tumor warrant aggressive local radiation combined with typically 2 or 3 years of neoadjuvant/concurrent/adjuvant ADT. Fit men in the high-risk group can consider 6 cycles of docetaxel without prednisone after EBRT is completed and while continuing ADT. The combination of EBRT and brachytherapy, with or without neoadjuvant/concurrent/adjuvant ADT, is another primary treatment option. However, the optimal duration of ADT in this setting remains unclear.

Radical prostatectomy with PLND remains an option because a subset of younger and healthier men in the high-risk group may benefit from operation.

### Very High Risk

Patients at very high risk (locally advanced) are defined by the NCCN Guidelines as men with clinical stage T3b to T4, primary Gleason pattern 5, or more than 4 biopsy cores with Gleason score 8 to 10/Gleason grade group 4-5.<sup>430</sup> The options for this group include: 1) EBRT and long-term ADT (category 1); 2) EBRT plus brachytherapy with or without long-term ADT; 3) radical prostatectomy plus PLND in younger, healthier patients with no tumor fixation to the pelvic side wall; or 4) ADT or observation for patients not candidates for definitive therapy. Fit men in the high-risk group can consider 6 cycles of docetaxel without prednisone after EBRT is completed and while continuing ADT.

### Nodal and Metastatic Disease

ADT or EBRT of the primary tumor plus 2 or 3 years of neoadjuvant/concurrent/adjuvant ADT are options for patients

diagnosed with N1 disease on presentation. Positive nodal disease identified during radical prostatectomy is addressed under *Adjuvant or Salvage Therapy after Radical Prostatectomy*. Analysis of data from the control arm of STAMPEDE supports the use of EBRT with ADT in men with node-positive, non-metastatic disease.<sup>431</sup> Two-year failure-free survival was improved with the planned use of radiation in this subset of trial participants (53% vs. 81%; HR, 0.48; 95% CI, 0.29–0.79).

ADT is recommended for patients with M1 cancer.

### Disease Monitoring

#### *Patients on Active Surveillance*

For patients who choose active surveillance, an appropriate active surveillance schedule includes PSA measurement no more often than every 6 months unless clinically indicated, DRE no more often than every 12 months unless clinically indicated, and repeat prostate biopsy no more often than every 12 months unless clinically indicated. A repeat prostate biopsy within 6 months of diagnosis is indicated if the initial biopsy was less than 10 cores or if assessment results show discordance.

Reliable parameters of prostate cancer progression await the results of ongoing clinical trials. Change in prostate exam or increase in PSA level may prompt consideration for repeat biopsy at the discretion of the physician. Repeat biopsy can be considered as often as annually to assess for disease progression. Repeat biopsies are not indicated when life expectancy is less than 10 years or when men are on observation. mpMRI may be considered to exclude the presence of anterior cancer if the PSA level rises and systematic prostate biopsy remains negative.<sup>432</sup> PSA doubling time is not considered reliable enough to be used alone to detect disease progression.<sup>433</sup>





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If repeat biopsy shows Gleason 4 or 5 disease, or if tumor is found in a greater number of biopsy cores or in a higher percentage of a given biopsy core, cancer progression may have occurred.

### ***Patients after Initial Definitive Therapy***

For patients initially treated with intent to cure, serum PSA levels should be measured every 6 to 12 months for the first 5 years and then annually. PSA testing every 3 months may be better for men at high risk of recurrence. When prostate cancer recurred after radical prostatectomy, Pound and colleagues found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 10 years.<sup>434</sup> Local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation. Therefore, annual DRE is appropriate to monitor for prostate cancer recurrence and to detect colorectal cancer. Similarly, after EBRT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually and a DRE is recommended annually. The clinician may opt to omit the DRE if PSA levels remain undetectable.

### ***Patients with Node-Positive or Metastatic Disease on ADT***

The intensity of clinical monitoring for patients presenting with lymph-node-positive or metastatic disease is determined by the response to initial ADT, radiotherapy, or both. Follow-up evaluation of these patients should include history and physical examination and PSA measurement every 3 to 6 months based on clinical judgment. The relative risk for bone metastasis or death increases as PSA doubling time (PSADT) falls; a major inflection point appears at PSADT of 8 months. Bone imaging should be performed more frequently in these men.<sup>435</sup>

Patients treated with either medical or surgical ADT have increased risk for osteoporosis. A baseline bone mineral density study should be

considered for these patients. Supplementation is recommended using calcium (500 mg) and vitamin D (400 IU). Men who are osteopenic/osteoporotic should be considered for denosumab, zoledronic acid, or alendronate.

### ***Patients under Observation***

Patients under observation should be monitored for symptom development at 6- to 12-month intervals. PSA, renal function, and red cell mass may be assessed.

### ***Adjuvant or Salvage Therapy after Radical Prostatectomy***

Most patients who have undergone radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult.

### ***Adjuvant Therapy***

Published trials provide high-level evidence that can be used to counsel patients more appropriately regarding the use of adjuvant therapy. Thompson and colleagues reported the results of SWOG 8794, which enrolled 425 men with extraprostatic cancer found at radical prostatectomy. Patients were randomized to receive either adjuvant EBRT or usual care, and follow-up has reached a median of 12.6 years.<sup>436</sup> The initial study report revealed that adjuvant EBRT reduced the risk of PSA relapse and disease recurrence.<sup>437</sup> An update reported improved 10-year biochemical failure-free survival for patients with high-risk disease (seminal vesicle positive) receiving post-prostatectomy adjuvant radiation compared to observation (36% vs. 12%;  $P = .001$ ).<sup>438</sup>

Another randomized trial conducted by EORTC<sup>439</sup> compared post-prostatectomy observation and adjuvant EBRT in 1005 patients. All patients had extraprostatic disease and/or positive surgical margins.





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The 5-year biochemical progression-free survival significantly improved with EBRT compared to observation for patients with positive surgical margins (78% vs. 49%), but benefit was not seen for patients with negative surgical margins.

A German study by Wiegel and colleagues reported results on 268 patients.<sup>440</sup> All participants had extraprostatic disease and undetectable PSA levels after radical prostatectomy. Postoperative radiation improved 5-year biochemical progression-free survival compared to observation alone (72% vs. 54%; HR, 0.53; 95% CI, 0.37–0.79). Collectively, these trial results suggest that continued follow-up of these series of patients may show a survival advantage.

Although observation after radical prostatectomy is appropriate, adjuvant EBRT after recuperation from operation is likely beneficial in men with one or more adverse laboratory or pathologic features, which include positive surgical margin, seminal vesicle invasion, and/or extracapsular extension as recommended in the guideline by the American Urological Association (AUA) and ASTRO.<sup>441</sup> Positive surgical margins are unfavorable, especially if diffuse (>10-mm margin involvement or ≥3 sites of positivity) or associated with persistent serum levels of PSA. The defined target volumes include the prostate bed.<sup>442</sup> The value of whole pelvic irradiation is unclear due to a lack of benefit in progression-free survival in 2 trials (RTOG 9413 and GETUG 01)<sup>443–445</sup>; whole pelvic radiation may be appropriate for selected patients.

Several management options should be considered if positive lymph nodes are found during or after radical prostatectomy. ADT is a category 1 option, as discussed above (see *Adjuvant ADT after Radical Prostatectomy*).<sup>339</sup> Another option is observation, which is a category 2A recommendation for patients with very-low-risk or low-risk prostate cancer but category 2B for patients with intermediate, high, or very high

risk. Retrospective data show that initial observation may be safe in some men with N1 disease at radical prostatectomy, because 28% of a cohort of 369 patients remained free from biochemical recurrence at 10 years.<sup>446</sup> A third option is the addition of pelvic EBRT to ADT (category 2B). This last recommendation is based on retrospective studies and a National Cancer Data Base analysis that demonstrated improved biochemical recurrence-free survival, cancer-specific survival, and all-cause survival with post-prostatectomy EBRT and ADT compared to adjuvant ADT alone in patients with lymph node metastases.<sup>447–450</sup>

### **Biochemical Recurrence After Radical Prostatectomy**

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time, and the presence or absence of positive surgical margins.<sup>451–455</sup> A large retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after radical prostatectomy<sup>454</sup> showed that the predictors of progression were Gleason score 8 to 10, pre-EBRT PSA level >2 ng/mL, seminal vesicle invasion, negative surgical margins, and PSA doubling time ≤10 months. However, prediction of systemic disease versus local recurrence and hence responsiveness to postoperative radiation has proven unfeasible for individual patients using clinical and pathologic criteria.<sup>456</sup> Delivery of adjuvant or salvage EBRT becomes both therapeutic and diagnostic—PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging, and a nomogram<sup>29,457</sup> may prove useful to predict response, but it has not been validated.

Men who suffer biochemical recurrence after radical prostatectomy fall into 3 groups: 1) those whose PSA level fails to fall to undetectable levels after radical prostatectomy (persistent disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a



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subsequent detectable PSA level that increases on 2 or more subsequent laboratory determinations (recurrent disease); or 3) the occasional case with persistent but low PSA levels attributed to slow PSA metabolism or residual benign tissue. Consensus has not defined a threshold level of PSA below which PSA is truly “undetectable.”<sup>80</sup> Group 3 does not require further evaluation until PSA increases. Since PSA elevation alone does not necessarily lead to clinical failure,<sup>458</sup> the workup for 1 and 2 must include an evaluation for distant metastases.

The specific staging tests depend on the clinical history, but usually include a combination of PSA doubling time assessment, TRUS biopsy, bone scan, and prostate MRI. Abdominal/pelvic CT/MRI and C-11 choline PET may be useful.

Bone scans are appropriate when patients develop symptoms or when PSA levels are increasing rapidly. In one study, the probability of a positive bone scan for a patient not on ADT after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL.<sup>459</sup> A TRUS biopsy may be helpful when imaging suggests local recurrence.

The patient may be observed or undergo primary salvage EBRT with or without ADT if distant metastases are not suspected during biochemical recurrence.<sup>441</sup> Large retrospective cohort studies support the use of EBRT in this setting, because it is associated with decreased all-cause and prostate cancer-specific survival.<sup>456,460</sup> The recommended post-radical prostatectomy EBRT dose is 64 to 72 Gy and may be increased for gross recurrence that has been proven by biopsy. The target volume includes the prostate bed and may include the whole pelvis in selected patients.<sup>442</sup> Treatment is most effective when pre-treatment PSA level is below 0.5 ng/mL.<sup>457</sup> Paradoxically, salvage EBRT was shown to be most beneficial when the PSA doubling time was <6 months in a cohort analysis of 635 men,<sup>456</sup> although another study of 519 men reported

mortality reduction for both men with PSA doubling time <6 months and those with PSA doubling time ≥6 months.<sup>460</sup> Most men with prolonged PSA doubling time may be observed safely.<sup>461</sup>

Six months of concurrent/adjuvant ADT can be coadministered with salvage radiation based on the results of GETUG-16.<sup>462</sup> An LHRH agonist should be used. Two years instead of 6 months of ADT can be considered in addition to radiation for men with persistent PSA after RP or for PSA levels that exceed 1.0 ng/mL at the time of initiation of salvage therapy, based on results of RTOG 9601.<sup>327</sup> For 2 years of ADT, level 1 evidence support 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.

ADT alone becomes the salvage treatment when there is proven or high suspicion for distant metastases. Radiation alone is not recommended but may be given to the site of metastasis or symptoms in addition to ADT in specific cases, such as to weight-bearing bone involvement. Observation remains acceptable for selected patients, with ADT delayed until symptoms develop or PSA levels suggest that symptoms are imminent. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient.

### Post-Irradiation Recurrence

The 2006 Phoenix definition was revised by ASTRO and the Radiation Therapy Oncology Group in Phoenix.<sup>463</sup> 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without hormonal therapy; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the rise above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid rise of PSA



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may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

Further workup is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical stage T1-2, life expectancy >10 years, and current PSA <10 ng/mL.<sup>464</sup> Workup typically includes PSA doubling time calculation, bone scan, and prostate MRI; additional tests, such as an abdominal/pelvic CT/MRI, TRUS biopsy, and/or C-11 choline PET can be considered. Local radiation failures are most responsive to salvage therapy when PSA levels at the time of treatment are low (<5 ng/mL). Biopsy should be encouraged at the time of radiation biochemical failure if staging workup does not reveal metastatic disease. Prostate biopsy in the setting of suspected local recurrence after radiation should be considered, including biopsy at the junction of the seminal vesicle and prostate, because this is a common site of treatment failure.

Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases to distant organs include observation or radical prostatectomy with PLND in selected cases by highly experienced surgeons. Other options for localized interventions include cryotherapy,<sup>465</sup> HIFU,<sup>297-300,303,304</sup> and brachytherapy (reviewed by Allen and colleagues<sup>466</sup> and discussed in *Salvage Brachytherapy*). Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with salvage therapy.

Negative TRUS biopsy after post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, and enrolling on clinical trials are viable options.

Patients with radiographic evidence of distant metastases or patients who are not initial candidates for local therapy should be treated with ADT or observed.

### Progressive Castration-Naïve Disease

The term "castration-naïve" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naïve" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function. Options for patients with progressive castration-naïve disease depend on the presence of distant metastases. Men with M0 disease can undergo orchiectomy or ADT with LHRH antagonist or combined androgen blockade or they can be observed until symptoms develop or are imminent. Options for men with M1 disease include: 1) orchiectomy; 2) LHRH agonist with or without anti-androgen for at least 7 days to prevent flare; 3) LHRH antagonist; 4) combined androgen blockade; or 5) ADT and docetaxel (75 mg/m<sup>2</sup>) with or without prednisone for 6 cycles. The last option of upfront docetaxel and ADT is based on results from the phase 3 CHAARTED and STAMPEDE trials (as discussed under *Docetaxel*).<sup>412,413</sup>

Docetaxel should not be offered to men with M0 progressive castration-naïve prostate cancer based on results of a pre-planned subgroup analysis of the STAMPEDE trial that showed no overall survival benefit for participants with M0 disease.<sup>412</sup> Men with low-volume metastatic disease can be offered early treatment with docetaxel combined with ADT; however they have less certain benefit from treatment than men with higher-volume disease, as this subgroup did not have definitively improved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).<sup>413,467,468</sup> Meta-analyses of randomized controlled trials also concluded that docetaxel provides a



significant OS benefit in this setting, with no evidence that the benefit was dependent on the volume of disease.<sup>469,470</sup>

In the setting of biochemical relapse after local therapy, one should first determine whether or not the patient is a candidate for salvage therapy. Men who opt for ADT should consider the intermittent approach. The timing of ADT initiation should be individualized according to PSA velocity, patient anxiety, and potential side effects. Patients with shorter PSA doubling time or rapid PSA velocity and long life expectancy should be encouraged to consider early ADT. Men with prolonged PSA doubling times who are older are excellent candidates for observation.

Patients with metastatic disease should be queried about adverse effects related to ADT. Intermittent ADT should be used for those who experience significant side effects of ADT. Some men who have no ADT-related morbidity may find the uncertainty of intermittent ADT not worthwhile. Intermittent ADT requires close monitoring of PSA and testosterone levels, especially during off-treatment periods, and patients may need to switch to continuous therapy upon signs of disease progression.

Combined androgen blockade therapy adds to cost and side effects, and prospective randomized evidence is lacking that combined androgen blockade is more efficacious than ADT.

### Progression to CRPC

Patients whose disease progresses to CRPC during primary ADT should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL; <1.7 nmol/L). Imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, overall patient health, PSA velocity, and Gleason grade.

A number of options for systemic therapy should be considered based on metastasis status, as discussed in the following sections.

### CRPC without Signs of Metastasis

Clinical trial is the preferred choice for patients with CRPC and no signs of distant metastasis (M0). Observation is another option, especially if PSA doubling time is ≥10 months since these patients will have a relatively indolent disease history.<sup>471</sup> Secondary hormone therapy is an option mainly for patients with shorter PSA doubling time (<10 months), because the androgen receptor may remain active. Patients whose disease progresses on combined androgen blockade should have the anti-androgen discontinued to exclude an “anti-androgen withdrawal response.”<sup>472,473</sup> Secondary hormone therapy can be an anti-androgen for patients who initially received medical or surgical castration, anti-androgen withdrawal, ketoconazole (adrenal enzyme inhibitor) with or without hydrocortisone, corticosteroid, diethylstilbestrol (DES), or other estrogen.<sup>474,475</sup> However, none of these strategies has yet been shown to prolong survival in randomized clinical trials in men who have not yet received docetaxel-based chemotherapy.

### Small Cell Carcinoma of the Prostate

Small cell carcinoma of the prostate should be considered in patients who no longer respond to ADT and test positive for metastases. Those with initial Gleason score 9 or 10/Gleason grade group 5 are especially at risk. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.<sup>476</sup> Biopsy of accessible metastatic lesions should be considered to identify patients with small cell histomorphologic features.<sup>477</sup> These cases may be managed by cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin).<sup>478,479</sup> Participation in a clinical trial is another option. Physicians should consult the [NCCN](#)



[Guidelines for Small Cell Lung Cancer](#) since the behavior of small cell carcinoma of the prostate is similar to that of small cell carcinoma of the lung. Small cell carcinomas of the prostate differ from neuroendocrine prostate cancers; the latter histology may be more common and should not alter treatment.

### Metastatic CRPC

All patients with metastatic CRPC should maintain castrate levels of serum testosterone (<50 ng/dL; <1.7 nmol/L) and receive best supportive care. Treatment options for specific settings are discussed below.

#### Bone Metastases

Zoledronic acid every 3 to 4 weeks or denosumab 120 mg every 4 weeks is recommended for men with CRPC and bone metastases to prevent or delay disease-associated SREs (category 1 recommendation). SREs include pathologic fractures, spinal cord compression, operation, or EBRT to bone. The optimal duration of zoledronic acid or denosumab in men with CRPC and bone metastases remains unclear.

Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of ONJ.<sup>480</sup> If invasive dental surgery is necessary, therapy should be deferred until the dentist confirms that the patient has healed completely from the dental procedure. Supplemental calcium and vitamin D are recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronic acid.

Monitoring of creatinine clearance is required to guide dosing of zoledronic acid. Zoledronic acid should be dose reduced in men with impaired renal function (estimated creatinine clearance 30–60 mL/min),

and held for creatinine clearance <30 mL/min.<sup>481</sup> Denosumab may be administered to men with impaired renal function or even men on hemodialysis; however, the risk for severe hypocalcemia and hypophosphatemia is greater, and the dose, schedule, and safety of denosumab have not yet been defined. A single study of 55 patients with creatinine clearance <30 mL/min or on hemodialysis evaluated the use of 60 mg dose denosumab.<sup>482</sup> Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with repletion as needed.

Clinical research continues on the prevention or delay of disease spread to bone. A phase 3 randomized trial of 1432 patients with non-metastatic CRPC at high risk of bone involvement showed that denosumab delayed bone metastasis by 4 months compared to placebo.<sup>483</sup> Overall survival was not improved, and the FDA did not approve this indication for denosumab.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.<sup>484</sup> Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.<sup>484</sup> Radium-223 can be used with denosumab or zoledronic acid.

The use of systemic radiotherapy with either 89Sr or 153Sm occasionally benefits patients with widely metastatic, painful, skeletal involvement that is not responding to palliative chemotherapy or systemic analgesia and who are not candidates for localized EBRT.<sup>286</sup> The risk of bone marrow suppression, which might influence the ability



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to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

### ***Asymptomatic or Minimally Symptomatic***

Based on phase 3 randomized trial evidence, sipuleucel-T is a category 1 recommendation for patients with metastatic CRPC who are asymptomatic or minimally symptomatic, and have good performance level (ECOG 0-1), estimated life expectancy >6 months, and no liver metastases.<sup>420</sup> Sipuleucel-T has not been studied in patients with visceral metastases. Clinicians and patients should be aware that the usual markers of benefit (decline in PSA and improvement in bone or CT scans) are not usually seen, and therefore benefit to the individual patient cannot be ascertained using currently available testing. Treatment subsequent to sipuleucel-T treatment should proceed as clinically indicated, particularly if symptoms develop.

### ***No Visceral Metastases***

Enzalutamide and abiraterone with prednisone are 2 newer therapies that received category 1 recommendation as first-line therapy for patients with asymptomatic, chemotherapy-naïve, metastatic CRPC. Abiraterone acetate should not be taken with food. Abiraterone acetate should be given with oral prednisone 5 mg twice daily to abrogate signs of mineralocorticoid excess that can result from treatment. These signs include hypertension, hypokalemia, and peripheral edema. Serum electrolytes and blood pressure should be monitored closely during therapy. Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.<sup>402</sup>

Docetaxel with prednisone is the traditional mainstay of treatment for symptomatic metastases (category 1). Docetaxel is not used commonly for asymptomatic patients, but may be considered when the patient shows signs of rapid progression or visceral metastases despite lack of

symptoms. Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases.

Other options include clinical trial participation and secondary hormone therapy (antiandrogen, antiandrogen withdrawal, ketoconazole with or without hydrocortisone, corticosteroid, DES, or other estrogens). Ketoconazole should not be used if the disease progressed on abiraterone; both drugs inhibit CYP17A1.

### ***Visceral Metastases***

Every-3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment for symptomatic CRPC with visceral metastases (category 1). PSA rise alone does not define docetaxel failure; the patient may benefit from continued chemotherapy if clinical progression is not apparent. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficiency and is not recommended.<sup>415</sup> Enzalutamide is another category 1 recommendation in this setting. Abiraterone has not been assessed formally in symptomatic men with CRPC prior to docetaxel. Therefore, its use in these patients is a category 2A recommendation. Use of abiraterone with prednisone is reasonable for men who are not candidates for docetaxel or who decline chemotherapy.

Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky lymph node metastases (>3–4 cm) and is not recommended in this setting.

Mitoxantrone may provide palliative benefit for symptomatic patients who cannot tolerate docetaxel.<sup>485,486</sup> Clinical trial and secondary hormone therapy are options.



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### ***Progression After Enzalutamide or Abiraterone***

Patients with disease progression after enzalutamide or abiraterone have the following options: docetaxel with prednisone (category 1), abiraterone with prednisone if previously given enzalutamide therapy, enzalutamide if previously given abiraterone, radium-223 for bone-predominant disease without visceral metastases (category 1), sipuleucel-T if asymptomatic or minimally symptomatic and without visceral or liver metastases (life expectancy >6 months and ECOG score 0–1), clinical trial, or secondary hormone therapy. All patients can continue through all treatment options and should receive best supportive care.

No randomized trials that compare taxane chemotherapies versus novel hormonal therapies in this setting have been reported. One molecular biomarker that may aid appropriate selection of therapy is the presence of androgen receptor splice variant 7 (AR-V7) in circulating tumor cells (CTCs).<sup>487</sup> Lack of response of men with metastatic CRPC to abiraterone and enzalutamide was associated with detection of AR-V7 mRNA in CTCs using an RNA-based polymerase chain reaction (PCR) assay.<sup>488</sup> AR-V7 presence did not preclude clinical benefit from taxane chemotherapies (docetaxel and cabazitaxel).<sup>489</sup> Men with AR-V7–positive CTCs exhibited superior progression-free survival with taxanes compared to novel hormonal therapies (abiraterone and enzalutamide); the two classes of agents resulted in comparable progression-free survival in men with AR-V7–negative CTCs. A confirmatory study used a different CTC assay that detected nuclear-localized AR-V7 protein using immunofluorescence. Men with AR-V7–positive CTCs had superior overall survival with taxanes versus abiraterone or enzalutamide, whereas overall survival was not different between the two classes of agents among patients with AR-V7–negative CTCs.<sup>490</sup>

These single-center clinical experiences suggest that AR-V7 assays are promising predictors of abiraterone and enzalutamide resistance, but they have not yet been validated prospectively and externally.

Furthermore, the prevalence of AR-V7 positivity is only 3% in patients prior to treatment with enzalutamide, abiraterone, and taxanes,<sup>490</sup> so the panel believes AR-V7 detection would not be useful to inform treatment decisions in the naïve setting. On the other hand, the prevalence of AR-V7 positivity is higher after abiraterone or enzalutamide failure (19%–39%<sup>488</sup>), but data have already shown that abiraterone/enzalutamide crossover therapy is rarely effective and taxanes are more effective in this setting. Therefore, the panel does not recommend use of these tests to determine treatment selection at this time.

### ***Progression After Docetaxel***

No consensus exists for the best additional therapy for patients with metastatic CRPC after docetaxel failure. Options include abiraterone with prednisone (category 1), enzalutamide (category 1), radium-223 for symptomatic bone metastases without visceral metastases (category 1), cabazitaxel with prednisone (category 1), sipuleucel-T if asymptomatic or minimally symptomatic and without visceral or liver metastases (life expectancy >6 months and ECOG score 0–1), clinical trial, docetaxel rechallenge, alternative chemotherapy (mitoxantrone), and secondary ADT. All patients can continue through all treatment options and should receive best supportive care.

Both abiraterone/prednisone and enzalutamide represent a new standard of care after failure of docetaxel chemotherapy for metastatic CRPC (category 1), provided these agents were not used before docetaxel.

The NCCN Guidelines Panel included cabazitaxel as an option for second-line therapy after docetaxel failure for patients with symptomatic





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metastatic CRPC. This recommendation is category 1 based on randomized phase 3 study data; however, extension of survival is relatively short and side effects are relatively high.<sup>416</sup> Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pre-treated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis), and symptom-directed antidiarrheal agents. Cabazitaxel has not been tested in patients with hepatic dysfunction and therefore should not be used in these patients. Cabazitaxel should be stopped upon clinical disease progression or intolerance.

The decision to initiate therapy in the post-docetaxel CRPC setting should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to these agents should be considered. No data inform the proper sequence for delivery of these agents in men with metastatic CRPC, and some data suggest cross-resistance between abiraterone and enzalutamide.<sup>491-493</sup> No randomized trials have been reported that compared these agents, and no predictive models or biomarkers help to identify patients who are likely to benefit from any of these agents. Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects. NCCN recommends that patients be closely monitored with radiological imaging (ie, CT, bone scan), PSA tests, and clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerability in cases where PSA or bone scan changes may indicate flare rather than true clinical progression.<sup>494,495</sup> The sequential use of these agents is reasonable in a patient who remains a candidate for further systemic therapy.

NCCN panelists agreed that docetaxel rechallenge may be useful in some patients (category 2A instead of category 1 in this setting), especially in those who have not shown definitive evidence of progression on prior docetaxel therapy. Some patients with metastatic CRPC may be deemed unsuitable for taxane chemotherapy; such patients could be considered for radium-223 or a second-line hormonal agent. In addition, mitoxantrone remains a palliative treatment option for men who are not candidates for taxane-based therapy based on older randomized studies that showed palliative benefit.<sup>485,486</sup> No chemotherapy regimen has demonstrated improved survival or quality of life after cabazitaxel, although several systemic agents other than mitoxantrone have shown palliative and radiographic response benefits in clinical trials (ie, carboplatin, cyclophosphamide, doxorubicin, vinorelbine, carboplatin/etoposide, docetaxel/carboplatin, gemcitabine/oxaliplatin, paclitaxel/carboplatin<sup>496-505</sup>). Prednisone or dexamethasone at low doses may provide palliative benefits in the chemotherapy-refractory setting.<sup>506</sup> No survival benefit for combination regimens over sequential single-agent regimens has been demonstrated, and toxicity is higher with combination regimens. Treatment with these agents could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care. Participation in a clinical trial is encouraged.

In the phase 3 sipuleucel-T trial, 18.2% of patients had received prior chemotherapy, which included docetaxel, since eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month prior to enrollment.<sup>420</sup> These men were asymptomatic or minimally symptomatic. In a subset analysis, both those who did and those who





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did not receive prior chemotherapy benefited from sipuleucel-T treatment.

### Summary

The intention of these guidelines is to provide a framework on which to base treatment decisions. Prostate cancer is a complex disease, with

many controversial aspects of management and with a dearth of sound data to support many treatment recommendations. Several variables (including adjusted life expectancy, disease characteristics, predicted outcomes, and patient preferences) must be considered by the patient and physician to tailor prostate cancer therapy for the individual patient.

Discussion  
update in  
progress



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**Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis**

Test	Platform	Populations Studied	Outcome Reported (Test independently predicts)	References	Molecular Diagnostic Services Program (MolDX) Recommendations
<b>Decipher</b>	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	Metastasis Prostate cancer-specific mortality	142,507-518	Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis Biochemical failure		
		Post RP, adjuvant or salvage radiotherapy	Metastasis		
<b>Ki-67</b>	IHC	Biopsy, intermediate- to high-risk treated with EBRT	Metastasis	519-522	Not recommended
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
<b>Oncotype DX Prostate</b>	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non-organ-confined pT3 or Gleason grade 4 disease on RP	63,523	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
<b>Prolaris</b>	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	Prostate cancer-specific mortality	59-62,524,525	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	Biochemical recurrence Metastasis		
		Biopsy, intermediate-risk treated with EBRT	Biochemical failure		
		RP, node-negative localized prostate cancer	Biochemical recurrence		
<b>ProMark</b>	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non-organ-confined pT3 or Gleason pattern 4 disease on RP	526	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
<b>PTEN</b>	Fluorescent in situ hybridization or IHC	TURP, conservatively managed (active surveillance)	Prostate cancer-specific mortality	527-531	Not recommended
		Biopsy, Gleason grade 3+3	Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	Biochemical recurrence		



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**Table 2. Selected Active Surveillance Experiences in North America**

Center	Toronto <sup>99,147,160</sup>	Johns Hopkins <sup>101,145,148,149</sup>	UCSF <sup>146</sup>	UCSF (newer cohort) <sup>532</sup>	Canary PASS <sup>163</sup>
No. patients	993	1298	321	810	905
Median age (y)	68	66	63	62	63
Median follow-up (months)	77	60	43	60	28
Overall survival	80% (10-y)	93% (10-y)	98% (10-y)	98% (5-y)	-
Cancer-specific survival	98% (10-y)	99.9% (10-y)	100% (5-y)	-	-
Conversion to treatment	36.5% (10-y)	50% (10-y)	24% (3-y)	40% (5-y)	19% (28-mo)
<b>Reason for treatment (% of entire cohort)</b>					
Gleason grade change	9.5%	15.1%	38%	-	-
PSA increase	11.7%*	-	26%†	-	-
Positive lymph node	-	0.4%	-	-	-
Personal choice	-1.6%	8%	8%	-	-
* PSA doubling time <3 years					
† PSA velocity >0.75 ng/mL/year					



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### References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28055103>.
2. Herget KA, Patel DP, Hanson HA, et al. Recent decline in prostate cancer incidence in the United States, by age, stage, and Gleason score. Cancer Med 2015;5:136-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26628287>.
3. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst 2015;107:djv048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25825511>.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26742998>.
5. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: [http://www.nlm.nih.gov/bsd/bsd\\_key.html](http://www.nlm.nih.gov/bsd/bsd_key.html). Accessed February 17, 2017.
6. Social Security Administration. Period Life Table. 2013. Available at: <https://www.ssa.gov/OACT/STATS/table4c6.html>. Accessed February 17, 2017.
7. Life Tables By Country. World Health Organization; Available at: <http://apps.who.int/gho/data/view.main.60000?lang=en>. Accessed February 17, 2017.
8. Howard DH. Life expectancy and the value of early detection. J Health Econ 2005;24:891-906. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16129128>.
9. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999;17:168-172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10458230>.
10. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 2002;95:281-286. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12124827>.
11. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-974. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9749478>.
12. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26492179>.
13. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016;69:428-435. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26166626>.
14. Loeb S, Folkvaljon Y, Robinson D, et al. Evaluation of the 2015 Gleason grade groups in a nationwide population-based cohort. Eur Urol 2016;69:1135-1141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26707871>.
15. Ham WS, Chalfin HJ, Feng Z, et al. New prostate cancer grading system predicts long-term survival following surgery for Gleason score 8-10 prostate cancer. Eur Urol 2016;71:907-912. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27876305>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

16. Mathieu R, Moschini M, Beyer B, et al. Prognostic value of the new grade groups in prostate cancer: a multi-institutional European validation study. *Prostate Cancer Prostatic Dis* 2017;20:197-202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28071673>.
17. Leapman MS, Cowan JE, Simko J, et al. Application of a prognostic Gleason grade grouping system to assess distant prostate cancer outcomes. *Eur Urol* 2016;71:750-759. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27940155>.
18. He J, Albertsen PC, Moore D, et al. Validation of a contemporary five-tiered Gleason grade grouping using population-based data. *Eur Urol* 2016;71:760-763. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27939073>.
19. Reese AC, Pierorazio PM, Han M, Partin AW. Contemporary evaluation of the National Comprehensive Cancer Network prostate cancer risk classification system. *Urology* 2012;80:1075-1079. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22995570>.
20. Muralidhar V, Chen MH, Reznor G, et al. Definition and validation of "favorable high-risk prostate cancer": implications for personalizing treatment of radiation-managed patients. *Int J Radiat Oncol Biol Phys* 2015;93:828-835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26530751>.
21. Dinh KT, Muralidhar V, Mahal BA, et al. Occult high-risk disease in clinically low-risk prostate cancer with  $\geq 50\%$  positive biopsy cores: should national guidelines stop calling them low-risk? *Urology* 2015;87:125-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26391387>.
22. Dinh KT, Mahal BA, Ziehr DR, et al. Incidence and predictors of upgrading and up staging among 10,000 contemporary patients with low risk prostate cancer. *J Urol* 2015;194:343-349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25681290>.
23. Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013;64:895-902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23541457>.
24. Johns Hopkins Medicine. The Partin Tables. Available at: [http://urology.jhu.edu/prostate/partin\\_tables.php](http://urology.jhu.edu/prostate/partin_tables.php) Accessed February 17, 2017.
25. Makarov DV, Trock BJ, Humphreys EB, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095-1101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17572194>.
26. Borque A, Rubio-Briones J, Esteban LM, et al. Implementing the use of nomograms by choosing threshold points in predictive models: 2012 updated Partin Tables vs a European predictive nomogram for organ-confined disease in prostate cancer. *BJU Int* 2014;113:878-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24529282>.
27. Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. *J Urol* 2003;170:1792-1797. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14532778>.
28. Wong LM, Neal DE, Finelli A, et al. Evaluation of models predicting insignificant prostate cancer to select men for active surveillance of prostate cancer. *Prostate Cancer Prostatic Dis* 2015;18:137-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25667108>.
29. Memorial Sloan-Kettering Cancer Center. Prostate Cancer Nomograms. Available at: <http://www.mskcc.org/mskcc/html/10088.cfm>. Accessed February 17, 2017.
30. Punnen S, Freedland SJ, Presti JC, Jr., et al. Multi-institutional validation of the CAPRA-S score to predict disease recurrence and



mortality after radical prostatectomy. Eur Urol 2014;65:1171-1177.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23587869>.

31. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006;98:715-717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16705126>.

32. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009;27:4300-4305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19636023>.

33. Graefen M, Haese A, Pichlmeier U, et al. A validated strategy for side specific prediction of organ confined prostate cancer: a tool to select for nerve sparing radical prostatectomy. J Urol 2001;165:857-863. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11176486>.

34. Ohori M, Kattan MW, Koh H, et al. Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. J Urol 2004;171:1844-1849; discussion 1849. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15076291>.

35. Steuber T, Graefen M, Haese A, et al. Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol 2006;175:939-944; discussion 944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16469587>.

36. Briganti A, Chun FK, Salonia A, et al. A nomogram for staging of exclusive nonobturator lymph node metastases in men with localized prostate cancer. Eur Urol 2007;51:112-119; discussion 119-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16806662>.

37. Cagiannos I, Karakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003;170:1798-1803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14532779>.

38. Kattan MW, Potters L, Blasko JC, et al. Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. Urology 2001;58:393-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11549487>.

39. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol 2008;179:S20-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18405743>.

40. Potters L, Roach M, 3rd, Davis BJ, et al. Postoperative nomogram predicting the 9-year probability of prostate cancer recurrence after permanent prostate brachytherapy using radiation dose as a prognostic variable. Int J Radiat Oncol Biol Phys 2010;76:1061-1065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19540064>.

41. Zelefsky MJ, Kattan MW, Fearn P, et al. Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. Urology 2007;70:283-287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17826490>.

42. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801-808. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16478903>.

43. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol 1999;17:1499-1507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10334537>.

44. Ondracek RP, Kattan MW, Murekeyisoni C, et al. Validation of the Kattan nomogram for prostate cancer recurrence after radical prostatectomy. J Natl Compr Canc Netw 2016;14:1395-1401. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27799510>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

45. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27528718>.

46. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999;353:267-272. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9929018>.

47. Khoo VS. Radiotherapeutic techniques for prostate cancer, dose escalation and brachytherapy. Clin Oncol (R Coll Radiol) 2005;17:560-571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16238144>.

48. D'Amico AV, Cote K, Loffredo M, et al. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol 2002;20:4567-4573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12454114>.

49. Abdollah F, Karnes RJ, Suardi N, et al. Predicting survival of patients with node-positive prostate cancer following multimodal treatment. Eur Urol 2014;65:554-562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24094576>.

50. D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003;95:1376-1383. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/13130113>.

51. Royce TJ, Chen MH, Wu J, et al. Surrogate end points for all-cause mortality in men with localized unfavorable-risk prostate cancer treated with radiation therapy vs radiation therapy plus androgen deprivation therapy: a secondary analysis of a randomized clinical trial. JAMA Oncol 2017;3:652-658. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28097317>.

52. Committee on the Review of Omics-based Tests for Predicting Patient Outcomes in Clinical Trials, Institute of Medicine. Evolution of

translational omics, lessons learned and the path forward. 2012. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK202165/>. Accessed February 17, 2017.

53. Hayes DF. From genome to bedside: are we lost in translation? Breast 2013;22 Suppl 2:S22-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074786>.

54. Hayes DF. OMICS-based personalized oncology: if it is worth doing, it is worth doing well! BMC Med 2013;11:221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24228698>.

55. Maurice MJ, Abouassaly R, Kim SP, Zhu H. Contemporary nationwide patterns of active surveillance use for prostate cancer. JAMA Intern Med 2015;175:1569-1571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26121305>.

56. Maurice MJ, Kim SP, Abouassaly R. Current status of prostate cancer diagnosis and management in the United States. JAMA Oncol 2016;2:1505-1507. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27356204>.

57. Womble PR, Montie JE, Ye Z, et al. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. Eur Urol 2015;67:44-50. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25159890>.

58. Cher ML, Dhir A, Aufferberg GB, et al. Appropriateness criteria for active surveillance of prostate cancer. J Urol 2017;197:67-74. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27422298>.

59. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014;192:409-414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24508632>.

60. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in





# NCCN Guidelines Version 1.2018

## Prostate Cancer

patients with prostate cancer: a retrospective study. *Lancet Oncol* 2011;12:245-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21310658>.

61. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer* 2012;106:1095-1099. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22361632>.

62. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;86:848-853. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23755923>.

63. Klein EA, Cooperberg MR, Carroll PR. Reply to Yuri Tolkach, Markus Kuczyk, Florian Imkamp's Letter to the Editor re: Eric A. Klein, Matthew R. Cooperberg, Cristina Magi-Galluzzi, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol* 2014;66:550-60. *Eur Urol* 2014;66:e117-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25150174>.

64. Zhao SG, Chang SL, Spratt DE, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. *Lancet Oncol* 2016;17:1612-1620. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27743920>.

65. Sinnott JA, Peisch SF, Tyekucheva S, et al. Prognostic utility of a new mRNA expression signature of Gleason score. *Clin Cancer Res* 2017;23:81-87. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27663590>.

66. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375:443-453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27433846>.

67. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015;161:1215-1228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26000489>.

68. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33:244-250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25366685>.

69. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015;373:1697-1708. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26510020>.

70. Imyanitov EN, Moiseyenko VM. Drug therapy for hereditary cancers. *Hered Cancer Clin Pract* 2011;9:5. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21819606>.

71. Hager S, Ackermann CJ, Joerger M, et al. Anti-tumour activity of platinum compounds in advanced prostate cancer-a systematic literature review. *Ann Oncol* 2016;27:975-984. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27052650>.

72. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol* 2015;68:186-193. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25454609>.

73. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013;31:1748-1757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23569316>.

74. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. *Eur Urol* 2016;71:740-747. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27989354>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

75. Risko R, Merdan S, Womble PR, et al. Clinical predictors and recommendations for staging computed tomography scan among men with prostate cancer. *Urology* 2014;84:1329-1334. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25288575>.
76. Merdan S, Womble PR, Miller DC, et al. Toward better use of bone scans among men with early-stage prostate cancer. *Urology* 2014;84:793-798. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25096341>.
77. Kane CJ, Amling CL, Johnstone PA, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. *Urology* 2003;61:607-611. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12639656>.
78. Martino P, Scattoni V, Galosi AB, et al. Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). *World J Urol* 2011;29:595-605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21553276>.
79. Dotan ZA, Bianco FJ, Jr., Rabbani F, et al. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. *J Clin Oncol* 2005;23:1962-1968. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15774789>.
80. Koulikov D, Mohler MC, Mehedint DC, et al. Low detectable prostate specific antigen after radical prostatectomy--treat or watch? *J Urol* 2014;192:1390-1396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24859441>.
81. Shinghal R, Yemoto C, McNeal JE, Brooks JD. Biochemical recurrence without PSA progression characterizes a subset of patients after radical prostatectomy. Prostate-specific antigen. *Urology* 2003;61:380-385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12597952>.
82. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. *J Urol* 2011;186:1818-1824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21944089>.
83. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol* 2013;64:713-719. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23787357>.
84. Rastinehad AR, Turkbey B, Salami SS, et al. Improving detection of clinically significant prostate cancer: magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. *J Urol* 2013;191:1749-1754. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24333515>.
85. Wysock JS, Rosenkrantz AB, Huang WC, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol* 2014;66:343-351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24262102>.
86. Somford DM, Hamoen EH, Futterer JJ, et al. The predictive value of endorectal 3 Tesla multiparametric magnetic resonance imaging for extraprostatic extension in patients with low, intermediate and high risk prostate cancer. *J Urol* 2013;190:1728-1734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23680307>.
87. Park BH, Jeon HG, Jeong BC, et al. Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. *J Urol* 2014;192:82-88. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24440235>.
88. Pasoglou V, Larbi A, Collette L, et al. One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI):



# NCCN Guidelines Version 1.2018

## Prostate Cancer

toward an upfront simplified "all-in-one" imaging approach? Prostate 2014;74:469-477. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24375774>.

89. Heck MM, Souvatzoglou M, Retz M, et al. Prospective comparison of computed tomography, diffusion-weighted magnetic resonance imaging and [11C]choline positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer patients. Eur J Nucl Med Mol Imaging 2014;41:694-701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24297503>.

90. Lecouvet FE, El Mouedden J, Collette L, et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol 2012;62:68-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22366187>.

91. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. Eur J Nucl Med Mol Imaging 2015;43:55-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26450693>.

92. Reske SN, Blumstein NM, Neumaier B, et al. Imaging prostate cancer with 11C-choline PET/CT. J Nucl Med 2006;47:1249-1254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16883001>.

93. Umbehre MH, Muntener M, Hany T, et al. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: a systematic review and meta-analysis. Eur Urol 2013;64:106-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23628493>.

94. Walsh L, Shore R, Auvinen A, et al. Risks from CT scans--what do recent studies tell us? J Radiol Prot 2014;34:E1-5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24594968>.

95. American College of Radiology. ACR Manual on Contrast Media v10.2. 2016. Available at: <https://www.acr.org/Quality-Safety/Resources/Contrast-Manual>. Accessed February 17, 2017.

96. American College of Radiology. ACR Appropriateness Criteria. Available at: <http://www.acr.org/quality-safety/appropriateness-criteria>. Accessed February 17, 2017.

97. Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997;277:467-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9020270>.

98. Loeb S, Folkvaljon Y, Makarov DV, et al. Five-year nationwide follow-up study of active surveillance for prostate cancer. Eur Urol 2015;67:233-238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24993868>.

99. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25512465>.

100. Roemeling S, Roobol MJ, de Vries SH, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol 2007;51:1244-1250; discussion 1251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17161520>.

101. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379-3385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26324359>.

102. van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008;54:1297-1305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18342430>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

103. Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. *Eur Urol* 2015;67:993-1005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25616709>.

104. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415-1424. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27626136>.

105. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375:1425-1437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27626365>.

106. Carter G, Clover K, Britton B, et al. Wellbeing during Active Surveillance for localised prostate cancer: a systematic review of psychological morbidity and quality of life. *Cancer Treat Rev* 2015;41:46-60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25467109>.

107. Jeldres C, Cullen J, Hurwitz LM, et al. Prospective quality-of-life outcomes for low-risk prostate cancer: Active surveillance versus radical prostatectomy. *Cancer* 2015;121:2465-2473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25845467>.

108. Parker PA, Davis JW, Latini DM, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int* 2015;117:469-477. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25714186>.

109. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. *Cancer* 2009;115:3868-3878. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19637245>.

110. Pham KN, Cullen J, Hurwitz LM, et al. Prospective quality of life in men choosing active surveillance compared to those biopsied but not diagnosed with prostate cancer. *J Urol* 2016;196:392-398. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26976206>.

111. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo* 1994;8:439-443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7803731>.

112. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004;350:2239-2246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15163773>.

113. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;366:981-990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22417251>.

114. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19297566>.

115. Klotz L. Active surveillance for prostate cancer: for whom? *J Clin Oncol* 2005;23:8165-8169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16278468>.

116. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310-1319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19297565>.

117. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-1202. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20357281>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

118. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22228146>.

119. Sandblom G, Varenhorst E, Rosell J, et al. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011;342:d1539. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21454449>.

120. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725-732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20598634>.

121. Godtman RA, Holmberg E, Khatami A, et al. Long-term results of active surveillance in the Goteborg randomized, population-based prostate cancer screening trial. Eur Urol 2016;70:760-766. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27090975>.

122. Miller DC, Gruber SB, Hollenbeck BK, et al. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst 2006;98:1134-1141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16912266>.

123. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009;101:374-383. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19276453>.

124. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95:868-878. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12813170>.

125. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c)

prostate cancer. JAMA 1994;271:368-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7506797>.

126. Bastian PJ, Mangold LA, Epstein JI, Partin AW. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer 2004;101:2001-2005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15372478>.

127. Jeldres C, Suardi N, Walz J, et al. Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. Eur Urol 2008;54:1306-1313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18083294>.

128. Chun FK, Haese A, Ahyai SA, et al. Critical assessment of tools to predict clinically insignificant prostate cancer at radical prostatectomy in contemporary men. Cancer 2008;113:701-709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18553365>.

129. Bastian PJ, Carter BH, Bjartell A, et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. Eur Urol 2009;55:1321-1330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19286302>.

130. Sanda MG, Kaplan ID. A 64-year-old man with low-risk prostate cancer: review of prostate cancer treatment. JAMA 2009;301:2141-2151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19417179>.

131. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. CA Cancer J Clin 2016;66:290-308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26910411>.

132. Sundi D, Ross AE, Humphreys EB, et al. African American men With very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol 2013;31:2991-2997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23775960>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

133. Vora A, Large T, Aronica J, et al. Predictors of Gleason score upgrading in a large African-American population. *Int Urol Nephrol* 2013;45:1257-1262. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23864415>.

134. Abern MR, Bassett MR, Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate Center. *Prostate Cancer Prostatic Dis* 2013;16:85-90. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23069729>.

135. Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. *J Urol* 2012;187:1594-1599. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22425088>.

136. Sundi D, Faisal FA, Trock BJ, et al. Reclassification rates are higher among African American men than Caucasians on active surveillance. *Urology* 2015;85:155-160. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25440814>.

137. Faisal FA, Sundi D, Cooper JL, et al. Racial disparities in oncologic outcomes after radical prostatectomy: long-term follow-up. *Urology* 2014;84:1434-1441. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25432835>.

138. Kovtun KA, Chen MH, Braccioforte MH, et al. Race and mortality risk after radiation therapy in men treated with or without androgen-suppression therapy for favorable-risk prostate cancer. *Cancer* 2016;122:3608-3614. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27490845>.

139. Pettaway CA, Troncso P, Ramirez EI, et al. Prostate specific antigen and pathological features of prostate cancer in black and white patients: a comparative study based on radical prostatectomy specimens. *J Urol* 1998;160:437-442. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9679893>.

140. Powell IJ, Dyson G, Land S, et al. Genes associated with prostate cancer are differentially expressed in African American and European American men. *Cancer Epidemiol Biomarkers Prev* 2013;22:891-897. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23515145>.

141. Sundi D, Kryvenko ON, Carter HB, et al. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. *J Urol* 2014;191:60-67. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23770146>.

142. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. *J Clin Oncol* 2015;33:2789-2796. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26195723>.

143. Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and biochemical outcomes among African-American and caucasian men with low risk prostate cancer in the SEARCH Database: implications for active surveillance candidacy. *J Urol* 2016;196:1408-1414. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27352635>.

144. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015;313:390-397. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25626035>.

145. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol* 2007;178:2359-2364; discussion 2364-2355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17936806>.

146. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer* 2008;112:2664-2670. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18433013>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

147. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28:126-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19917860>.

148. Sheridan TB, Carter HB, Wang W, et al. Change in prostate cancer grade over time in men followed expectantly for stage T1c disease. J Urol 2008;179:901-904; discussion 904-905. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18207195>.

149. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185-2190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21464416>.

150. Loblaw A, Zhang L, Lam A, et al. Comparing prostate specific antigen triggers for intervention in men with stable prostate cancer on active surveillance. J Urol 2010;184:1942-1946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20846681>.

151. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 2010;28:2810-2816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20439642>.

152. Bonekamp D, Bonekamp S, Mullins JK, et al. Multiparametric magnetic resonance imaging characterization of prostate lesions in the active surveillance population: incremental value of magnetic resonance imaging for prediction of disease reclassification. J Comput Assist Tomogr 2013;37:948-956. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24270118>.

153. Mullins JK, Bonekamp D, Landis P, et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. BJU Int 2013;111:1037-1045. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23464904>.

154. Nassiri N, Margolis DJ, Natarajan S, et al. Targeted biopsy to detect Gleason score upgrading during active surveillance for men with low versus intermediate risk prostate cancer. J Urol 2016;197:632-639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27639713>.

155. Ma TM, Tosoian JJ, Schaeffer EM, et al. The role of multiparametric magnetic resonance imaging/ultrasound fusion biopsy in active surveillance. Eur Urol 2017;71:174-180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27236496>.

156. Recabal P, Assel M, Sjoberg DD, et al. The efficacy of multiparametric magnetic resonance imaging and magnetic resonance imaging targeted biopsy in risk classification for patients with prostate cancer on active surveillance. J Urol 2016;196:374-381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26920465>.

157. Tran GN, Leapman MS, Nguyen HG, et al. Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance. Eur Urol 2016;72:275-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27595378>.

158. Klotz L. Point: active surveillance for favorable risk prostate cancer. J Natl Compr Canc Netw 2007;5:693-698. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17692173>.

159. Jain S, Loblaw A, Vesprini D, et al. Gleason upgrading with time in a large prostate cancer active surveillance cohort. J Urol 2015;194:79-84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25660208>.

160. Yamamoto T, Musunuru B, Vesprini D, et al. Metastatic prostate cancer in men initially treated with active surveillance. J Urol 2016;195:1409-1414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26707510>.

161. Tosoian JJ, Sundi D, Trock BJ, et al. Pathologic outcomes in favorable-risk prostate cancer: comparative analysis of men electing active surveillance and immediate surgery. Eur Urol 2015;69:576-581. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26456680>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

162. Dall'Era MA, Cowan JE, Simko J, et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU Int* 2011;107:1232-1237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20804478>.

163. Newcomb LF, Thompson IM, Jr., Boyer HD, et al. Outcomes of active surveillance for the management of clinically localized prostate cancer in the prospective, multi-institutional Canary PASS cohort. *J Urol* 2015;195:313-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26327354>.

164. Filippou P, Welty CJ, Cowan JE, et al. Immediate versus delayed radical prostatectomy: updated outcomes following active surveillance of prostate cancer. *Eur Urol* 2015;68:458-463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26138041>.

165. Feliciano J, Teper E, Ferrandino M, et al. The incidence of fluoroquinolone resistant infections after prostate biopsy--are fluoroquinolones still effective prophylaxis? *J Urol* 2008;179:952-955; discussion 955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18207185>.

166. Fujita K, Landis P, McNeil BK, Pavlovich CP. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. *J Urol* 2009;182:2664-2669. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19836757>.

167. Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst* 2008;100:1144-1154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18695132>.

168. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;370:932-942. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24597866>.

169. Pierorazio PM, Ross AE, Lin BM, et al. Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy. *BJU Int* 2012;110:1122-1128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22373045>.

170. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. *Eur Urol* 2012;61:961-971. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22280856>.

171. Shekarriz B, Upadhyay J, Pontes JE. Salvage radical prostatectomy. *Urol Clin North Am* 2001;28:545-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11590813>.

172. Klein EA, Bianco FJ, Serio AM, et al. Surgeon experience is strongly associated with biochemical recurrence after radical prostatectomy for all preoperative risk categories. *J Urol* 2008;179:2212-2216; discussion 2216-2217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18423716>.

173. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med* 2002;346:1138-1144. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11948274>.

174. Herrell SD, Smith JA, Jr. Robotic-assisted laparoscopic prostatectomy: what is the learning curve? *Urology* 2005;66:105-107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16194715>.

175. Smith JA, Jr., Herrell SD. Robotic-assisted laparoscopic prostatectomy: do minimally invasive approaches offer significant advantages? *J Clin Oncol* 2005;23:8170-8175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16278469>.

176. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*





# NCCN Guidelines Version 1.2018

## Prostate Cancer

2009;302:1557-1564. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19826025>.

177. Gandaglia G, Sammon JD, Chang SL, et al. Comparative effectiveness of robot-assisted and open radical prostatectomy in the postdissemination era. *J Clin Oncol* 2014;32:1419-1426. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24733797>.

178. Parsons JK, Bennett JL. Outcomes of retropubic, laparoscopic, and robotic-assisted prostatectomy. *Urology* 2008;72:412-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18267330>.

179. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol* 2012;62:405-417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22749852>.

180. Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol* 2012;62:418-430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22749850>.

181. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016;388:1057-1066. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27474375>.

182. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368:436-445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23363497>.

183. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol* 2014;15:223-231. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24440474>.

184. Freire MP, Weinberg AC, Lei Y, et al. Anatomic bladder neck preservation during robotic-assisted laparoscopic radical prostatectomy: description of technique and outcomes. *Eur Urol* 2009;56:972-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19781848>.

185. Abel EJ, Masterson TA, Warner JN, et al. Nerve-sparing prostatectomy and urinary function: a prospective analysis using validated quality-of-life measures. *Urology* 2009;73:1336-1340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19362347>.

186. Davis JW, Chang DW, Chevray P, et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. *Eur Urol* 2009;55:1135-1143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18783876>.

187. Leyh-Bannurah SR, Budaus L, Pompe R, et al. North American population-based validation of the National Comprehensive Cancer Network practice guideline recommendation of pelvic lymphadenectomy in contemporary prostate cancer. *Prostate* 2017;77:542-548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28093788>.

188. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. *Eur Urol* 2009;55:1251-1265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19297079>.

189. Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. *Eur Urol* 2007;52:29-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17448592>.

190. Masterson TA, Bianco FJ, Jr., Vickers AJ, et al. The association between total and positive lymph node counts, and disease progression in clinically localized prostate cancer. *J Urol* 2006;175:1320-1324; discussion 1324-1325. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16515989>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

191. Joslyn SA, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. *Urology* 2006;68:121-125. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16806432>.

192. Allaf ME, Palapattu GS, Trock BJ, et al. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. *J Urol* 2004;172:1840-1844. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15540734>.

193. Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? *J Urol* 2003;169:849-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12576797>.

194. Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. *J Urol* 2004;172:2252-2255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15538242>.

195. Wagner M, Sokoloff M, Daneshmand S. The role of pelvic lymphadenectomy for prostate cancer--therapeutic? *J Urol* 2008;179:408-413. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18076938>.

196. Fossati N, Willemse PM, van den Bergh RC, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol* 2017;72:84-109. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28126351>.

197. Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. *Int J Radiat Oncol Biol Phys* 2001;49:51-59. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11163497>.

198. Koper PC, Stroom JC, van Putten WL, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *Int J Radiat Oncol Biol Phys* 1999;43:727-734. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10098427>.

199. Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. *Int J Radiat Oncol Biol Phys* 2010;76:14-22. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19577865>.

200. Jacobs BL, Zhang Y, Schroeck FR, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *JAMA* 2013;309:2587-2595. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23800935>.

201. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124-1129. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18313526>.

202. Jani AB, Su A, Correa D, Gratzle J. Comparison of late gastrointestinal and genitourinary toxicity of prostate cancer patients undergoing intensity-modulated versus conventional radiotherapy using localized fields. *Prostate Cancer Prostatic Dis* 2007;10:82-86. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16983394>.

203. Jacobs BL, Zhang Y, Skolarus TA, et al. Comparative effectiveness of external-beam radiation approaches for prostate cancer. *Eur Urol* 2012;65:162-168. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22790288>.

204. Goldin GH, Sheets NC, Meyer AM, et al. Comparative effectiveness of intensity-modulated radiotherapy and conventional conformal radiotherapy in the treatment of prostate cancer after radical prostatectomy. *JAMA Intern Med* 2013;173:1136-1143. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23689844>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

205. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-1996. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16648499>.

206. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-1105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12128107>.

207. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294:1233-1239. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16160131>.

208. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17765406>.

209. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;15:464-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24581940>.

210. Denham JW, Steigler A, Joseph D, et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. *Radiother Oncol* 2015;115:301-307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26072289>.

211. Kalbasi A, Li J, Berman A, et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. *JAMA Oncol* 2015;1:897-906. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26181727>.

212. Xu N, Rossi PJ, Jani AB. Toxicity analysis of dose escalation from 75.6 Gy to 81.0 Gy in prostate cancer. *Am J Clin Oncol* 2011;34:11-15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20101167>.

213. Eade TN, Hanlon AL, Horwitz EM, et al. What dose of external-beam radiation is high enough for prostate cancer? *Int J Radiat Oncol Biol Phys* 2007;68:682-689. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17398026>.

214. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;31:3860-3868. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24101042>.

215. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1172-1178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22537541>.

216. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;17:1061-1069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27339116>.

217. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17:1047-1060. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27339115>.

218. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol* 2016;34:2325-2332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27044935>.



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## Prostate Cancer

219. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol* 2015;16:274-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25656287>.

220. Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. *Eur J Cancer* 2015;51:2345-2367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26254809>.

221. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004;96:1358-1367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15367568>.

222. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-1261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18354103>.

223. Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;92:971-977. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26054865>.

224. Nguyen PL, D'Amico AV, Lee AK, Suh WW. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure: a systematic review of the literature. *Cancer* 2007;110:1417-1428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17694553>.

225. Critz FA, Benton JB, Shrake P, Merlin ML. 25-Year disease-free survival rate after irradiation for prostate cancer calculated with the prostate specific antigen definition of recurrence used for radical

prostatectomy. *J Urol* 2013;189:878-883. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23103235>.

226. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010;11:1066-1073. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20933466>.

227. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61:1285-1290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15817329>.

228. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol* 2015;33:2143-2150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25691677>.

229. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011;378:2104-2111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22056152>.

230. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;373:301-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19091394>.

231. Fossa SD, Wiklund F, Klepp O, et al. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of the Scandinavian Prostate Cancer Group-7. *Eur Urol* 2016;70:684-691. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27025586>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

232. Dasu A. Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? Clin Oncol (R Coll Radiol) 2007;19:289-301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17517328>.

233. Buyyounouski MK, Price RA, Jr., Harris EE, et al. Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. Int J Radiat Oncol Biol Phys 2010;76:1297-1304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20338473>.

234. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol 2011;6:3. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21219625>.

235. Kang JK, Cho CK, Choi CW, et al. Image-guided stereotactic body radiation therapy for localized prostate cancer. Tumori 2011;97:43-48. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21528663>.

236. Madsen BL, Hsi RA, Pham HT, et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. Int J Radiat Oncol Biol Phys 2007;67:1099-1105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17336216>.

237. Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol 2013;8:58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23497695>.

238. Katz AJ, Santoro M, Diblasio F, Ashley R. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. Radiat Oncol 2013;8:118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23668632>.

239. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol

2013;109:217-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24060175>.

240. Yu JB, Cramer LD, Herrin J, et al. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. J Clin Oncol 2014;32:1195-1201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24616315>.

241. Hannan R, Tumati V, Xie XJ, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. Eur J Cancer 2016;59:142-151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27035363>.

242. Halpern JA, Sedrakyan A, Hsu WC, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer 2016;122:2496-2504. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27224858>.

243. Brachman DG, Thomas T, Hilbe J, Beyer DC. Failure-free survival following brachytherapy alone or external beam irradiation alone for T1-2 prostate tumors in 2222 patients: results from a single practice. Int J Radiat Oncol Biol Phys 2000;48:111-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10924979>.

244. Masson S, Persad R, Bahl A. HDR brachytherapy in the management of high-risk prostate cancer. Adv Urol 2012;2012:980841. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22461791>.

245. Spratt DE, Soni PD, McLaughlin PW, et al. American Brachytherapy Society Task Group Report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer. Brachytherapy 2017;16:1-12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27771243>.

246. Merrick GS, Butler WM, Wallner KE, et al. Permanent interstitial brachytherapy in younger patients with clinically organ-confined prostate cancer. Urology 2004;64:754-759. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15491715>.





# NCCN Guidelines Version 1.2018

## Prostate Cancer

247. Eade TN, Horwitz EM, Ruth K, et al. A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or (125)I permanent implant. *Int J Radiat Oncol Biol Phys* 2008;71:338-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18207665>.

248. Wong WW, Vora SA, Schild SE, et al. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. *Cancer* 2009;115:5596-5606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19670452>.

249. Lee N, Wu CS, Brody R, et al. Factors predicting for postimplantation urinary retention after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1457-1460. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11121648>.

250. Henkel TO, Kahmann F. Permanent brachytherapy: prostate seed implants as an out-patient treatment. *Arch Ital Urol Androl* 2000;72:295-301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11221059>.

251. Nag S, Bice W, DeWyngaert K, et al. The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2000;46:221-230. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10656396>.

252. Al-Salihi O, Mitra A, Payne H. Challenge of dose escalation in locally advanced unfavourable prostate cancer using HDR brachytherapy. *Prostate Cancer Prostatic Dis* 2006;9:370-373. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16832383>.

253. Fang FM, Wang YM, Wang CJ, et al. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. *Jpn J Clin Oncol* 2008;38:474-479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18621848>.

254. Pieters BR, van de Kamer JB, van Herten YR, et al. Comparison of biologically equivalent dose-volume parameters for the treatment of prostate cancer with concomitant boost IMRT versus IMRT combined with brachytherapy. *Radiother Oncol* 2008;88:46-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18378028>.

255. Soumarova R, Homola L, Perkova H, Stursa M. Three-dimensional conformal external beam radiotherapy versus the combination of external radiotherapy with high-dose rate brachytherapy in localized carcinoma of the prostate: comparison of acute toxicity. *Tumori* 2007;93:37-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17455870>.

256. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192-1199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15718316>.

257. Hoskin PJ, Motohashi K, Bownes P, et al. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol* 2007;84:114-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17531335>.

258. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217-222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22341794>.

259. Shen X, Keith SW, Mishra MV, et al. The impact of brachytherapy on prostate cancer-specific mortality for definitive radiation therapy of high-grade prostate cancer: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2012;83:1154-1159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22270175>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

260. Bittner N, Merrick GS, Butler WM, et al. Long-term outcome for very high-risk prostate cancer treated primarily with a triple modality approach to include permanent interstitial brachytherapy. *Brachytherapy* 2012;11:250-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22436516>.

261. Martinez-Monge R, Moreno M, Ciervide R, et al. External-beam radiation therapy and high-dose rate brachytherapy combined with long-term androgen deprivation therapy in high and very high prostate cancer: preliminary data on clinical outcome. *Int J Radiat Oncol Biol Phys* 2012;82:e469-476. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22284039>.

262. D'Amico AV, Moran BJ, Braccioforte MH, et al. Risk of death from prostate cancer after brachytherapy alone or with radiation, androgen suppression therapy, or both in men with high-risk disease. *J Clin Oncol* 2009;27:3923-3928. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19597029>.

263. Demanes DJ, Brandt D, Schour L, Hill DR. Excellent results from high dose rate brachytherapy and external beam for prostate cancer are not improved by androgen deprivation. *Am J Clin Oncol* 2009;32:342-347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19398902>.

264. Dattoli M, Wallner K, True L, et al. Long-term outcomes for patients with prostate cancer having intermediate and high-risk disease, treated with combination external beam irradiation and brachytherapy. *J Oncol* 2010;2010. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20847945>.

265. Hoskin P. High dose rate brachytherapy for prostate cancer. *Cancer Radiother* 2008;12:512-514. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18755623>.

266. Grills IS, Martinez AA, Hollander M, et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. *J Urol* 2004;171:1098-1104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14767279>.

267. Vargas C, Ghilezan M, Hollander M, et al. A new model using number of needles and androgen deprivation to predict chronic urinary toxicity for high or low dose rate prostate brachytherapy. *J Urol* 2005;174:882-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16093980>.

268. Aaronson DS, Yamasaki I, Gottschalk A, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. *BJU Int* 2009;104:600-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19245439>.

269. Yamada Y, Kollmeier MA, Pei X, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. *Brachytherapy* 2014;13:111-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24373762>.

270. Georg D, Hopfgartner J, Gora J, et al. Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2014;88:715-722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24521685>.

271. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:e201-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21621343>.

272. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst* 2013;105:25-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23243199>.

273. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer*



# NCCN Guidelines Version 1.2018

## Prostate Cancer

2014;120:1076-1082. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24382757>.

274. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012;307:1611-1620. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22511689>.

275. American Society of Radiation Oncology (ASTRO). Proton Beam Therapy Model Policy. 2014. Available at:  
[https://www.astro.org/uploadedFiles/Main\\_Site/Practice\\_Management/R reimbursement/ASTRO%20PBT%20Model%20Policy%20FINAL.pdf](https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/R reimbursement/ASTRO%20PBT%20Model%20Policy%20FINAL.pdf). Accessed February 17, 2017.

276. American Society of Radiation Oncology (ASTRO). Proton Beam Therapy for Prostate Cancer Position Statement. Available at:  
<https://www.astro.org/Proton-Beam-Therapy-for-Prostate-Cancer-Position-Statement.aspx>. Accessed February 17, 2017.

277. Konski A, James J, Hartsell W, et al. Economic analysis of radiation therapy oncology group 97-14: multiple versus single fraction radiation treatment of patients with bone metastases. Am J Clin Oncol 2009;32:423-428. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19546803>.

278. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798-804. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15928300>.

279. Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15:164-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24369114>.

280. Janjan N, Lutz ST, Bedwinek JM, et al. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of

Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. J Palliat Med 2009;12:417-426. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19416037>.

281. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213-223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23863050>.

282. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol 2014;15:1397-1406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25439694>.

283. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014;15:738-746. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24836273>.

284. Nilsson S, Cisko P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. Ann Oncol 2016;27:868-874. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26912557>.

285. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. Lancet Oncol 2016;17:1306-1316. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27473888>.

286. Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. J Nucl Med 2004;45:1358-1365. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15299062>.





287. Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol 2008;180:1993-2004. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18817934>.

288. Bahn D, de Castro Abreu AL, Gill IS, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol 2012;62:55-63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22445223>.

289. Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer 2010;116:323-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19937954>.

290. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer 2009;115:4695-4704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19691092>.

291. Chin JL, Al-Zahrani AA, Autran-Gomez AM, et al. Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). J Urol 2012;188:1170-1175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22901586>.

292. de Castro Abreu AL, Bahn D, Leslie S, et al. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU Int 2013;112:298-307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23826840>.

293. Eisenberg ML, Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. Urology 2008;72:1315-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18597824>.

294. Li YH, Elshafei A, Agarwal G, et al. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. Prostate 2015;75:1-7. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25283814>.

295. Rischmann P, Gelet A, Riche B, et al. Focal high intensity focused ultrasound of unilateral localized prostate cancer: a prospective multicentric hemiablation study of 111 patients. Eur Urol 2017;71:267-273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27720531>.

296. Albisinni S, Aoun F, Bellucci S, et al. Comparing high-intensity focal ultrasound hemiablation to robotic radical prostatectomy in the management of unilateral prostate cancer: a matched-pair analysis. J Endourol 2017;31:14-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27799004>.

297. Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer 2012;118:4148-4155. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22907704>.

298. Baco E, Gelet A, Crouzet S, et al. Hemi salvage high-intensity focused ultrasound (HIFU) in unilateral radiorecurrent prostate cancer: a prospective two-centre study. BJU Int 2014;114:532-540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24930692>.

299. Crouzet S, Murat FJ, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol 2012;105:198-202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23068708>.

300. Uddin Ahmed H, Cathcart P, Chalasani V, et al. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer 2012;118:3071-3078. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22071795>.





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301. Crouzet S, Blana A, Murat FJ, et al. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients. *BJU Int* 2017;119:896-904. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28063191>.

302. Palermo G, Totaro A, Sacco E, et al. High intensity focused ultrasound as first line salvage therapy in prostate cancer local relapse after radical prostatectomy: 4-year follow-up outcomes. *Minerva Urol Nefrol* 2017;69:93-100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27681490>.

303. Shah TT, Peters M, Kanthabalan A, et al. PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure. *Prostate Cancer Prostatic Dis* 2016;19:311-316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27431499>.

304. Siddiqui KM, Billia M, Arifin A, et al. Pathological, oncologic and functional outcomes of a prospective registry of salvage high intensity focused ultrasound ablation for radiorecurrent prostate cancer. *J Urol* 2016;197:97-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27422297>.

305. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. *Eur Urol* 2013;63:618-622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23265382>.

306. Azzouzi AR, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2016;18:181-191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28007457>.

307. Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial

of intermittent versus continuous ADT. *J Clin Oncol* 2015;33:1151-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25732157>.

308. Trachtenberg J, Gittleman M, Steidle C, et al. A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol* 2002;167:1670-1674. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11912385>.

309. Labrie F, Dupont A, Belanger A, Lachance R. Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. *J Urol* 1987;138:804-806. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3309363>.

310. Schulze H, Senge T. Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. *J Urol* 1990;144:934-941. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2144596>.

311. Kolinsky M, de Bono JS. The ongoing challenges of targeting the androgen receptor. *Eur Urol* 2016;69:841-843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26585581>.

312. Sun M, Choueiri TK, Hamnvik OP, et al. Comparison of gonadotropin-releasing hormone agonists and orchiectomy: effects of androgen-deprivation therapy. *JAMA Oncol* 2016;2:500-507. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26720632>.

313. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25:1596-1605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17404365>.

314. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Prostate Cancer Trialists'*



Collaborative Group. Lancet 2000;355:1491-1498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10801170>.

315. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002;95:361-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12124837>.

316. Laufer M, Denmeade SR, Sinibaldi VJ, et al. Complete androgen blockade for prostate cancer: what went wrong? J Urol 2000;164:3-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10840412>.

317. Dijkstra S, Witjes WP, Roos EP, et al. The AVOCAT study: Bicalutamide monotherapy versus combined bicalutamide plus dutasteride therapy for patients with locally advanced or metastatic carcinoma of the prostate-a long-term follow-up comparison and quality of life analysis. Springerplus 2016;5:653. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27330919>.

318. Turo R, Smolski M, Esler R, et al. Diethylstilboestrol for the treatment of prostate cancer: past, present and future. Scand J Urol 2014;48:4-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24256023>.

319. Ockrim JL, Lalani EN, Laniado ME, et al. Transdermal estradiol therapy for advanced prostate cancer--forward to the past? J Urol 2003;169:1735-1737. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12686820>.

320. Langley RE, Cafferty FH, Alhasso AA, et al. Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). Lancet Oncol 2013;14:306-316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23465742>.

321. Gilbert DC, Duong T, Kynaston HG, et al. Quality-of-life outcomes from the Prostate Adenocarcinoma: TransCutaneous Hormones (PATCH) trial evaluating luteinising hormone-releasing hormone agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer. BJU Int 2016;119:667-675. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27753182>.

322. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. JAMA Intern Med 2014;174:1460-1467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25023796>.

323. Potosky AL, Haque R, Cassidy-Bushrow AE, et al. Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. J Clin Oncol 2014;32:1324-1330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24638009>.

324. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289-295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18212313>.

325. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 2011;12:451-459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21440505>.

326. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21751904>.

327. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417-428. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28146658>.



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328. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;26:585-591. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18172188>.

329. Bolla M, Maingon P, Carrie C, et al. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC trial 22991. *J Clin Oncol* 2016;34:1748-1756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26976418>.

330. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. *J Clin Oncol* 2015;33:332-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25534388>.

331. Rosenthal SA, Bae K, Pienta KJ, et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. *Int J Radiat Oncol Biol Phys* 2009;73:672-678. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18990504>.

332. Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: final results of Radiation Therapy Oncology Group phase 3 randomized trial NRG Oncology RTOG 9902. *Int J Radiat Oncol Biol Phys* 2015;93:294-302. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26209502>.

333. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292:821-827. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15315996>.

334. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15470214>.

335. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol* 2008;26:2497-2504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18413638>.

336. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360:2516-2527. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19516032>.

337. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015;16:320-327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25702876>.

338. Souhami L, Bae K, Pilepich M, Sandler H. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. *J Clin Oncol* 2009;27:2137-2143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19307511>.

339. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472-479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16750497>.

340. Wong YN, Freedland S, Egleston B, et al. Role of androgen deprivation therapy for node-positive prostate cancer. *J Clin Oncol* 2009;27:100-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19047295>.





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## Prostate Cancer

341. McLeod DG, Iversen P, See WA, et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006;97:247-254. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16430622>.

342. McLeod DG, See WA, Klimberg I, et al. The bicalutamide 150 mg early prostate cancer program: findings of the North American trial at 7.7-year median followup. *J Urol* 2006;176:75-80. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16753373>.

343. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol* 2016;17:727-737. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27155740>.

344. Shaw GL, Wilson P, Cuzick J, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. *BJU Int* 2007;99:1056-1065. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17346277>.

345. Akakura K, Bruchovsky N, Goldenberg SL, et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. *Cancer* 1993;71:2782-2790. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7682149>.

346. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367:895-903. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22931259>.

347. Higano CS. Intermittent versus continuous androgen deprivation therapy. *J Natl Compr Canc Netw* 2014;12:727-733. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24812139>.

348. Schulman C, Cornel E, Matveev V, et al. Intermittent versus continuous androgen deprivation therapy in patients with relapsing or locally advanced prostate cancer: a phase 3b randomised study

(ICELAND). *Eur Urol* 2015;69:720-727. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26520703>.

349. Dong Z, Wang H, Xu M, et al. Intermittent hormone therapy versus continuous hormone therapy for locally advanced prostate cancer: a meta-analysis. *Aging Male* 2015;18:233-237. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26225795>.

350. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341:1781-1788. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10588962>.

351. Schroder FH, Kurth KH, Fossa SD, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumour: final results of European Organisation for the Research and Treatment of Cancer protocol 30846 after 13 years of follow-up (a randomised controlled trial). *Eur Urol* 2009;55:14-22. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18823693>.

352. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol* 2006;24:3984-3990. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16921051>.

353. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013;368:1314-1325. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23550669>.

354. Botrel TE, Clark O, dos Reis RB, et al. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. *BMC Urol* 2014;14:9. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24460605>.





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356. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol 2013;31:2029-2036. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23630216>.

357. Hussain M, Tangen C, Higano C, et al. Evaluating intermittent androgen-deprivation therapy phase III clinical trials: the devil is in the details. J Clin Oncol 2015;34:280-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26552421>.

358. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int 2013;111:543-548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23351025>.

359. Gaztanaga M, Crook J. Androgen deprivation therapy: minimizing exposure and mitigating side effects. J Natl Compr Canc Netw 2012;10:1088-1095; quiz 1088, 1096. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22956808>.

360. Lapi F, Azoulay L, Niazi MT, et al. Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. JAMA 2013;310:289-296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23860987>.

361. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. J Clin Oncol 2015;33:2021-2027. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25964245>.

362. Nead KT, Gaskin G, Chester C, et al. Androgen deprivation therapy and future Alzheimer's Disease risk. J Clin Oncol 2015;34:566-571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26644522>.

363. Khosrow-Khavar F, Rej S, Yin H, et al. Androgen deprivation therapy and the risk of dementia in patients with prostate cancer. J Clin Oncol 2017;35:201-207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27870566>.

364. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15647578>.

365. Smith MR, Boyce SP, Moynour E, et al. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136-139; discussion 139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16406890>.

366. Smith MR, Lee WC, Brandman J, et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23:7897-7903. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16258089>.

367. Daniell HW, Dunn SR, Ferguson DW, et al. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol 2000;163:181-186. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10604342>.

368. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998;83:1561-1566. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9781950>.

369. Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol 1999;161:1219-1222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10081873>.



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370. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11575286>.

371. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599-603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11836291>.

372. National Osteoporosis Foundation. Learn about Osteoporosis. Available at: <http://nof.org/learn>. Accessed February 17, 2017.

373. World Health Organisation. WHO Fracture Risk Assessment Tool. Available at: <http://www.shef.ac.uk/FRAX/>. Accessed February 17, 2017.

374. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003;169:2008-2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12771706>.

375. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038-1042. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17369566>.

376. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med 2007;146:416-424. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17371886>.

377. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl

J Med 2009;361:745-755. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19671656>.

378. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448-4456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16983113>.

379. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420-2425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17557956>.

380. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24:1868-1876. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16622261>.

381. Tsai HK, D'Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516-1524. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17925537>.

382. Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol 2009;27:92-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19047297>.

383. Saigal CS, Gore JL, Krupski TL, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493-1500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17657815>.

384. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate



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cancer: a meta-analysis of randomized trials. JAMA 2011;306:2359-2366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22147380>.

385. Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol 2014;65:704-709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23433805>.

386. Schmid M, Sammon JD, Reznor G, et al. Dose-dependent effect of androgen deprivation therapy for localized prostate cancer on adverse cardiac events. BJU Int 2015;118:221-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26074405>.

387. O'Farrell S, Garmo H, Holmberg L, et al. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol 2015;33:1243-1251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25732167>.

388. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol 2014;32:335-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24344218>.

389. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002;167:2361-2367; discussion 2367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11992038>.

390. Tayek JA, Heber D, Byerley LO, et al. Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. Metabolism 1990;39:1314-1319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2123281>.

391. Dockery F, Bulpitt CJ, Agarwal S, et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond) 2003;104:195-201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12546642>.

392. Smith JC, Bennett S, Evans LM, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001;86:4261-4267. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11549659>.

393. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006;91:1305-1308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16434464>.

394. Eri LM, Urdal P, Bechensteen AG. Effects of the luteinizing hormone-releasing hormone agonist leuprolide on lipoproteins, fibrinogen and plasminogen activator inhibitor in patients with benign prostatic hyperplasia. J Urol 1995;154:100-104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7539852>.

395. Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164:217-227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14695335>.

396. Mohler JL, Gregory CW, Ford OH, 3rd, et al. The androgen axis in recurrent prostate cancer. Clin Cancer Res 2004;10:440-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14760063>.

397. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21612468>.





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398. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13:983-992. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22995653>.

399. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol* 2012;13:1210-1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23142059>.

400. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368:138-148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23228172>.

401. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015;16:152-160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25601341>.

402. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187-1197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22894553>.

403. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol* 2014;15:1147-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25104109>.

404. Food and Drug Administration. Enzalutamide label information. 2013. Available at:

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/203415s001lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203415s001lbl.pdf). Accessed February 17, 2017.

405. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424-433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24881730>.

406. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol* 2017;71:151-154. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27477525>.

407. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol* 2016;17:153-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26774508>.

408. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. *J Clin Oncol* 2016;34:2098-2106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26811535>.

409. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15470213>.

410. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008;26:242-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18182665>.

411. Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. *Lancet Oncol*





2013;14:117-124. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23294853>.

412. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-1177. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26719232>.

413. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737-746. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26244877>.

414. Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. *Lancet Oncol* 2015;16:787-794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26028518>.

415. Machiels JP, Mazzeo F, Clausse M, et al. Prospective randomized study comparing docetaxel, estramustine, and prednisone with docetaxel and prednisone in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2008;26:5261-5268. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18794543>.

416. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147-1154. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20888992>.

417. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol* 2013;24:2402-2408. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23723295>.

418. De Bono JS, Hardy-Bessard A-C, Kim C-S, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m<sup>2</sup> (C20) versus 25 mg/m<sup>2</sup> (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D) [abstract]. *ASCO Meeting Abstracts* 2016;34:5008. Available at:

<http://meetinglibrary.asco.org/content/169889-176>.

419. Sartor AO, Oudard S, Sengelov L, et al. Cabazitaxel vs docetaxel in chemotherapy-naïve (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA) [abstract]. *ASCO Meeting Abstracts* 2016;34:5006. Available at:

<http://meetinglibrary.asco.org/content/166318-176>.

420. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-422. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20818862>.

421. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-1468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12359855>.

422. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004;96:879-882. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15173273>.

423. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377:813-822. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21353695>.

424. Tarassoff P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofac Surg*



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2003;61:1238-1239. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14586868>.

425. Edge SB, Byrd DR, Compton CC, et al., eds. AJCC Cancer Staging Manual (ed 7th Edition). New York: Springer; 2010.

426. College of American Pathologists. Prostate Gland. 2006. Available at:

[http://www.cap.org/apps/docs/committees/cancer/cancer\\_protocols/2006/prostate06\\_pw.pdf](http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2006/prostate06_pw.pdf). Accessed February 17, 2017.

427. Briganti A, Passoni N, Ferrari M, et al. When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. Eur Urol 2010;57:551-558. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20034730>.

428. Wolf JS, Jr., Cher M, Dall'era M, et al. The use and accuracy of cross-sectional imaging and fine needle aspiration cytology for detection of pelvic lymph node metastases before radical prostatectomy. J Urol 1995;153:993-999. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7853590>.

429. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-213. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22808955>.

430. Sondi D, Wang VM, Pierorazio PM, et al. Very-high-risk localized prostate cancer: definition and outcomes. Prostate Cancer Prostatic Dis 2014;17:57-63. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24189998>.

431. James ND, Spears MR, Clarke NW, et al. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: data from patients in the control arm of the STAMPEDE trial. JAMA Oncol 2016;2:348-357. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26606329>.

432. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011;59:477-494. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21195536>.

433. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976-983. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22698574>

[http://www.europeanurology.com/article/S0302-2838\(12\)00691-4/pdf/active-surveillance-for-prostate-cancer-a-systematic-review-of-the-literature](http://www.europeanurology.com/article/S0302-2838(12)00691-4/pdf/active-surveillance-for-prostate-cancer-a-systematic-review-of-the-literature).

434. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-1597. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10235151>.

435. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800-3806. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24043751>.

436. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956-962. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19167731>.

437. Thompson IM, Jr., Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006;296:2329-2335. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17105795>.



# NCCN Guidelines Version 1.2018

## Prostate Cancer

438. Swanson GP, Goldman B, Tangen CM, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. *J Urol* 2008;180:2453-2457; discussion 2458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18930488>.

439. Van der Kwast TH, Bolla M, Van Poppel H, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. *J Clin Oncol* 2007;25:4178-4186. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17878474>.

440. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924-2930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19433689>.

441. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* 2013;190:441-449. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23707439>.

442. Michalski JM, Lawton C, El Naqa I, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;76:361-368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19394158>.

443. Lawton CA, DeSilvio M, Roach M, 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007;69:646-655. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17531401>.

444. Millar J, Boyd R, Sutherland J. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant

to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions: in regard to Lawton et al. (*Int J Radiat Oncol Biol Phys* 2007;69:646-655.). *Int J Radiat Oncol Biol Phys* 2008;71:316; author reply 316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18406900>.

445. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007;25:5366-5373. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18048817>.

446. Touijer KA, Mazzola CR, Sjoberg DD, et al. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol* 2014;65:20-25. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23619390>.

447. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014;32:3939-3947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25245445>.

448. Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol* 2009;55:1003-1011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19211184>.

449. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol* 2011;59:832-840. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21354694>.

450. Lin CC, Gray PJ, Jemal A, Efsthathiou JA. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. *J Natl Cancer Inst* 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25957435>.





# NCCN Guidelines Version 1.2018

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451. Cheung R, Kamat AM, de Crevoisier R, et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. *Int J Radiat Oncol Biol Phys* 2005;63:134-140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16111581>.

452. Lee AK, D'Amico AV. Utility of prostate-specific antigen kinetics in addition to clinical factors in the selection of patients for salvage local therapy. *J Clin Oncol* 2005;23:8192-8197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16278472>.

453. Patel R, Lepor H, Thiel RP, Taneja SS. Prostate-specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. *Urology* 2005;65:942-946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15882728>.

454. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291:1325-1332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15026399>.

455. Ward JF, Zincke H, Bergstralh EJ, et al. Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. *J Urol* 2004;172:2244-2248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15538240>.

456. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008;299:2760-2769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18560003>.

457. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25:2035-2041. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17513807>.

458. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. *Urology* 1999;54:884-890. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10565752>.

459. Cher ML, Bianco FJ, Jr., Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol* 1998;160:1387-1391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9751361>.

460. Cotter SE, Chen MH, Moul JW, et al. Salvage radiation in men after prostate-specific antigen failure and the risk of death. *Cancer* 2011;117:3925-3932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21437885>.

461. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol* 2005;23:4975-4979. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16051949>.

462. Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* 2016;17:747-756. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27160475>.

463. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965-974. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16798415>.

464. Rogers E, Ohori M, Kassabian VS, et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol* 1995;153:104-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7526002>.





# NCCN Guidelines Version 1.2018

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465. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. *BJU Int* 2007;100:760-764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17662081>.

466. Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. *Cancer* 2007;110:1405-1416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17685384>.

467. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:149-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23306100>.

468. Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. *Eur Urol* 2015;70:256-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26610858>.

469. Tucci M, Bertaglia V, Vignani F, et al. Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2015;69:563-573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26422676>.

470. Vale CL, Burdett S, Rydzewska LH, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol* 2015;17:243-256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26718929>.

471. Smith MR, Kabbavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic

prostate cancer. *J Clin Oncol* 2005;23:2918-2925. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15860850>.

472. Dupont A, Gomez JL, Cusan L, et al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. *J Urol* 1993;150:908-913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7688437>.

473. Sartor AO, Tangen CM, Hussain MH, et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer* 2008;112:2393-2400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18383517>.

474. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). *J Clin Oncol* 2004;22:1025-1033. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15020604>.

475. Oh WK, Kantoff PW, Weinberg V, et al. Prospective, multicenter, randomized phase II trial of the herbal supplement, PC-SPEs, and diethylstilbestrol in patients with androgen-independent prostate cancer. *J Clin Oncol* 2004;22:3705-3712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15289492>.

476. Brennan SM, Gregory DL, Stillie A, et al. Should extrapulmonary small cell cancer be managed like small cell lung cancer? *Cancer* 2010;116:888-895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20052730>.

477. Yao JL, Madeb R, Bourne P, et al. Small cell carcinoma of the prostate: an immunohistochemical study. *Am J Surg Pathol* 2006;30:705-712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16723847>.

478. Sella A, Konichezky M, Flex D, et al. Low PSA metastatic androgen-independent prostate cancer. *Eur Urol* 2000;38:250-254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10940696>.



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479. Spiess PE, Pettaway CA, Vakar-Lopez F, et al. Treatment outcomes of small cell carcinoma of the prostate: a single-center study. *Cancer* 2007;110:1729-1737. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17786954>.

480. Coleman RE. Risks and benefits of bisphosphonates. *Br J Cancer* 2008;98:1736-1740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18506174>.

481. Food and Drug Administration. Zometa (zoledronic acid) label information. 2011. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021223s027lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021223s027lbl.pdf). Accessed February 17, 2017.

482. Food and Drug Administration. Xgeva (denosumab) label information. 2010. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/125320s114s124lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125320s114s124lbl.pdf). Accessed February 17, 2017.

483. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012;379:39-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22093187>.

484. Food and Drug Administration. Radium-223 dichloride label information. 2013. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/203971lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf). Accessed February 17, 2017.

485. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-1764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8656243>.

486. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer:

results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999;17:2506-2513. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561316>.

487. Antonarakis ES, Armstrong AJ, Dehm SM, Luo J. Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. *Prostate Cancer Prostatic Dis* 2016;19:231-241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27184811>.

488. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* 2014;371:1028-1038. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25184630>.

489. Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. *JAMA Oncol* 2015;1:582-591. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26181238>.

490. Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. *JAMA Oncol* 2016;2:1441-1449. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27262168>.

491. Noonan KL, North S, Bitting RL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;24:1802-1807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23585511>.

492. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013;24:1807-1812. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23576708>.



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493. Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. *Eur J Cancer* 2014;50:78-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074764>.

494. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res* 2011;17:4854-4861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21632851>.

495. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016;34:1402-1418. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26903579>.

496. Abratt RP, Brune D, Dimopoulos MA, et al. Randomised phase III study of intravenous vinorelbine plus hormone therapy versus hormone therapy alone in hormone-refractory prostate cancer. *Ann Oncol* 2004;15:1613-1621. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15520061>.

497. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res* 2013;19:3621-3630. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649003>.

498. Beer TM, Garzotto M, Katovic NM. High-dose calcitriol and carboplatin in metastatic androgen-independent prostate cancer. *Am J Clin Oncol* 2004;27:535-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15596926>.

499. Cabrespine A, Guy L, Khenifar E, et al. Randomized Phase II study comparing paclitaxel and carboplatin versus mitoxantrone in patients with hormone-refractory prostate cancer. *Urology* 2006;67:354-359. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16442593>.

500. Harris KA, Harney E, Small EJ. Liposomal doxorubicin for the treatment of hormone-refractory prostate cancer. *Clin Prostate Cancer* 2002;1:37-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15046711>.

501. Ladoire S, Eymard JC, Zanetta S, et al. Metronomic oral cyclophosphamide prednisolone chemotherapy is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. *Anticancer Res* 2010;30:4317-4323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21036758>.

502. Lee JL, Ahn JH, Choi MK, et al. Gemcitabine-oxaliplatin plus prednisolone is active in patients with castration-resistant prostate cancer for whom docetaxel-based chemotherapy failed. *Br J Cancer* 2014;110:2472-2478. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24736579>.

503. Lloriot Y, Massard C, Gross-Goupil M, et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. *Ann Oncol* 2009;20:703-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19179557>.

504. Nakabayashi M, Sartor O, Jacobus S, et al. Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy in patients with metastatic hormone-refractory prostate cancer. *BJU Int* 2008;101:308-312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18184327>.

505. Torti FM, Aston D, Lum BL, et al. Weekly doxorubicin in endocrine-refractory carcinoma of the prostate. *J Clin Oncol* 1983;1:477-482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6668511>.

506. Shamash J, Powles T, Sarker SJ, et al. A multi-centre randomised phase III trial of dexamethasone vs dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: immediate vs deferred diethylstilbestrol. *Br J Cancer* 2011;104:620-628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21285990>.





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507. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One 2013;8:e66855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23826159>.
508. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-2053. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23770138>.
509. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol 2015;67:778-786. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25466945>.
510. Prensner JR, Zhao S, Erho N, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. Lancet Oncol 2014;15:1469-1480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25456366>.
511. Tomlins SA, Alshalalfa M, Davicioni E, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. Eur Urol 2015;68:555-567. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25964175>.
512. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. Eur Urol 2015;69:157-165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26058959>.
513. Cooperberg MR, Davicioni E, Crisan A, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol 2015;67:326-333. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24998118>.
514. Ross AE, Feng FY, Ghadessi M, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis 2014;17:64-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24145624>.
515. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int J Radiat Oncol Biol Phys 2014;89:1038-1046. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25035207>.
516. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 2015;33:944-951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25667284>.
517. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. Eur Urol 2016;70:588-596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26806658>.
518. Klein EA, Santiago-Jimenez M, Yousefi K, et al. Molecular analysis of low grade prostate cancer using a genomic classifier of metastatic potential. J Urol 2017;197:122-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27569435>.
519. Khor LY, Bae K, Paulus R, et al. MDM2 and Ki-67 predict for distant metastasis and mortality in men treated with radiotherapy and androgen deprivation for prostate cancer: RTOG 92-02. J Clin Oncol 2009;27:3177-3184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470936>.
520. Verhoven B, Yan Y, Ritter M, et al. Ki-67 is an independent predictor of metastasis and cause-specific mortality for prostate cancer patients treated on Radiation Therapy Oncology Group (RTOG) 94-08. Int J Radiat Oncol Biol Phys 2013;86:317-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23474109>.





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521. Li R, Heydon K, Hammond ME, et al. Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in radiation therapy oncology group protocol 86-10. Clin Cancer Res 2004;10:4118-4124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15217948>.

522. Fisher G, Yang ZH, Kudahetti S, et al. Prognostic value of Ki-67 for prostate cancer death in a conservatively managed cohort. Br J Cancer 2013;108:271-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23329234>.

523. Cullen J, Rosner IL, Brand TC, et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 2015;68:123-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25465337>.

524. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer 2015;113:382-389. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26103570>.

525. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol 2013;31:1428-1434. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23460710>.

526. Blume-Jensen P, Berman DM, Rimm DL, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. Clin Cancer Res 2015;21:2591-2600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25733599>.

527. Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. Br J Cancer 2013;108:2582-2589. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23695019>.

528. Lotan TL, Carvalho FL, Peskoe SB, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. Mod Pathol 2015;28:128-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24993522>.

529. Lotan TL, Gurel B, Sutcliffe S, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. Clin Cancer Res 2011;17:6563-6573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21878536>.

530. Lotan TL, Wei W, Ludkovski O, et al. Analytic validation of a clinical-grade PTEN immunohistochemistry assay in prostate cancer by comparison with PTEN FISH. Mod Pathol 2016;29:904-914. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27174589>.

531. Troyer DA, Jamaspishvili T, Wei W, et al. A multicenter study shows PTEN deletion is strongly associated with seminal vesicle involvement and extracapsular extension in localized prostate cancer. Prostate 2015;75:1206-1215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25939393>.

532. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol 2015;193:807-811. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25261803>.